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16. ABSTRACT

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This report reviews the extensive amount of dioxin literature that has become available in recent years. Although most published reports deal exclusively with the highly toxic dioxin 2,3,7,8-TCDD, some include information on other dioxins. These latter reports were sought out so that a document covering dioxins as a class of chemical compounds could be prepared.

A brief description of what is known about the chemistry of dioxins is presented first. Chemical reaction mechanisms by which dioxins may be formed are reviewed, particularly those likely to occur within commercially significant processes. Various routes of formation are identified in addition to the classical route of the hydrolysis of trichlorophenol. Basic organic chemicals and pesticides with a reasonable potential for dioxin byproduct contamination are surveyed as to current and past producers and production locations. Classifications are presented both for general organic chemicals and for pesticides that indicate likelihood of dioxin formation. Conditions are noted that are most likely to promote dioxin formation in various processes.

An analytical approach for use in quantifying part-per-trillion levels of TCDD's in various chemical wastes is included in this report. The Brehm Laboratory of Wright State University examined waste samples provided by the Environmental Protection Agency from plants manufacturing trichlorophenol, pentachlorophenol, and hexachlorophene, and from plants processing wood preservatives. The extraction procedure developed for isolating TCDD's from the various types of sample matrices is fully described. The analysis using highly specific and sensitive coupled gas chromatographic-mass spectrometric (GC-MS) methods is also described in detail. TCDD's were detected and quantitatively determined in several of the samples at levels in the ppt to ppm range.

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Reports on possible routes of degradation are characterized. Finally, current methods of disposal of dioxin-contaminated materials are described, and possible advanced techniques for ultimate disposal are outlined.

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DIOXINS

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FOREWORD

When energy and material resources are extracted, processed, converted, and used, the related pollutional impacts on our environment and even on our health often require that new and increasingly more efficient pollution control methods be used. The Industrial Environmental Research Laboratory-Cincinnati (IERL-Ci) assists in developing and demonstrating new and improved methodologies that will meet these needs both efficiently and economically.

This report deals with a group of hazardous chemical compounds known as dioxins. The extreme toxicity of one of these chemicals, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), has been a concern of both scientific researchers and the public for many years. The sheer mass of published information that has resulted from this concern has created difficulties in assessing the overall scope of the dioxin problem. In this report, the voluminous data on 2,3,7,8-TCDD and other dioxins are summarized and assembled in a manner that allows comparison of related observations from many sources; thus, the report serves as a comprehensive guide in evaluation of the environmental hazards of dioxins.

Sections 2 and 3 present detailed information on the chemistry and sources of dioxins. Various routes of formation of dioxins are discussed, and the possible presence of dioxins in basic organic chemicals and pesticides is addressed. Section 4 details the development of an analytical method for detecting part-per-trillion levels of dioxins in industrial wastes. Sections 5 through 8 discuss routes of human exposure to dioxins, including accounts of public and occupational exposure, and the health effects, environmental degradation, transport, and disposal of dioxins.

David G. Stephan
Director
Industrial Environmental Research Laboratory
Cincinnati

PREFACE

This report deals with a group of hazardous chemical compounds known as dioxins. The report discusses the detailed chemistry of dioxin formation and identifies types of organic chemicals and pesticides which may have dioxins associated with them as impurities or byproducts. It investigates the development of an analytical technique for identifying dioxins in industrial wastes. Finally, it summarizes the reported incidents of human exposure to dioxins, and examines the toxicity, environmental transport, and techniques available for decontamination and disposal of dioxin-contaminated material.

An extensive amount of literature published during the past 25 years has been concerned primarily with one extremely toxic member of this class of compounds, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Often described in both popular and technical literature as "TCDD" or simply "dioxin," this compound is one of the most toxic substances known to science. This report, however, is concerned not only with this compound, but also with all of its chemical relatives that contain the dioxin nucleus. Throughout this report, the term "TCDD's" is used to indicate the family of 22 tetrachlorodibenzo-*p*-dioxin isomers, whereas the term "dioxin" is used to indicate any compound with the basic dioxin nucleus. The most toxic isomer among those that have been assessed is specifically designated as "2,3,7,8-TCDD."

The objective in the use of these terms is to clarify a point of technical confusion that has occasionally hindered comparison of information from various sources. In particular, early laboratory analyses often reported the presence of "TCDD," which may have been the most-toxic 2,3,7,8-isomer or may have been a mixture of several of the tetrachloro isomers, some of which are relatively nontoxic. Throughout this report, the specific term 2,3,7,8-TCDD is used when it was the intent of the investigator to refer to this most-toxic isomer. Since early analytical methods could not dependably isolate specific isomers from environmental samples, the generic term "TCDD's" is used when this term appears to be most appropriate in light of present technology.

ABSTRACT

Concern about the potential contamination of the environment by dibenzo-*p*-dioxins through the use of certain chemicals and disposal of associated wastes prompted this study.

This report reviews the extensive amount of dioxin literature that has become available in recent years. Although most published reports deal exclusively with the highly toxic dioxin 2,3,7,8-TCDD, some include information on other dioxins. These latter reports were sought out so that a document covering dioxins as a class of chemical compounds could be prepared.

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An analytical approach for use in quantifying part-per-trillion levels of TCDD's in various chemical wastes is included in this report. The Brehm Laboratory of Wright State University examined waste samples provided by the Environmental Protection Agency from plants manufacturing trichlorophenol, pentachlorophenol, and hexachlorophene, and from plants processing wood preservatives. The extraction procedure developed for isolating TCDD's from the various types of sample matrices is fully described. The analysis using highly specific and sensitive coupled gas chromatographic-mass spectrometric (GC-MS) methods is also described in detail. TCDD's were detected and quantitatively determined in several of the samples at levels in the ppt to ppm range.

Incidents of human exposure to dioxins are reviewed and summarized. A review of the known health effects of 2,3,7,8-TCDD and other dioxins is presented. Many toxicological studies of the effects produced by chronic exposures to these toxicants and the possible mechanisms of action are described.

Reports on possible routes of degradation are characterized. Finally, current methods of disposal of dioxin-contaminated materials are described, and possible advanced techniques for ultimate disposal are outlined.

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LIST OF ABBREVIATIONS

cm	centimeter
DBDCDD's	dibromodichlorodibenzo-*p*-dioxins
DBDD's	dibromodibenzo-*p*-dioxins
DCDD's	dichlorodibenzo-*p*-dioxins
DDE	2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethylene
dioxins	dibenzo-*p*-dioxins
DFDD's	difluorodibenzo-*p*-dioxins
DMSO	dimethyl sulfoxide
DNDD's	dinitrodibenzo-*p*-dioxins
eV	electron volt
g	gram
GC	gas chromatography
GC-EC	gas chromatography-electron capture
GC-MS	gas chromatography-mass spectrometry
GC-MS-30	gas chromatography-mass spectrometry (high resolution)
GC-QMS	gas chromatography-quadrupole mass spectrometry (low resolution)
Hexa-CDD's	hexachlorodibenzo-*p*-dioxins
Hepta-CDD's	heptachlorodibenzo-*p*-dioxins
HPLC	high-pressure liquid chromatography
I.D.	inside diameter
kg	kilogram
LD_{50}	lethal dose to 50% of test group
m	meter
MCDD's	monochlorodibenzo-*p*-dioxins
m/e	mass to charge ratio
ml	milliliter
ml/min	milliliter/minute
mm	millimeter
MS	mass spectrometry
ng	nanogram
OBDD	octabromodibenzo-*p*-dioxin
OCDD	octachlorodibenzo-*p*-dioxin
PCB	polychlorinated biphenyl
PCP	pentachlorophenol
Penta-CDD's	pentachlorodibenzo-*p*-dioxins

(continued)

LIST OF ABBREVIATIONS (continued)

pg	picogram
ppb	parts per billion (μg/l or ng/ml)
ppm	parts per million (mg/l or μg/ml)
ppt	parts per trillion (ng/l or pg/ml)
psig	pounds per square inch gage
TBDD's	tetrabromodibenzo-*p*-dioxins
TCDD's	tetrachlorodibenzo-*p*-dioxins
TCP	trichlorophenol
Tri-CDD's	trichlorodibenzo-*p*-dioxins
2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
2,4,5-TCP	2,4,5-trichlorophenol
μg	microgram
UV	ultraviolet
V	volt

SECTION 1
INTRODUCTION

The growing concern with contamination of the environment by dioxins arises principally from their potential toxicity and their distribution as contaminants in commercial products. The purpose of this report is to present in a systematic and summary manner what is currently known about dioxins and their effects. Although most published reports deal exclusively with the highly toxic dioxin 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), some include information on other dioxins. These latter reports were sought out so that a document covering dioxins as a class of chemical compounds could be prepared.

Although 2,3,7,8-TCDD was first reported in the chemical literature in 1872, no major investigations into its toxicity were begun until the 1950's. Because of the remarkable stability of this substance in biological systems and its extreme toxicity, cumulative effects of extremely small doses are a major concern. For example, the LD_{50} of 2,3,7,8-TCDD for the male guinea pig has been shown to be only 0.6 μg/kg or 0.6 part per billion body weight (McConnell et al. 1978). Fetal mortality has been observed in rats that had been fed 10 consecutive doses of 2,3,7,8-TCDD at the level of 0.125 μg/kg per day (World Health Organization 1977). It is reasonable to presume, therefore, that the slightest trace of 2,3,7,8-TCDD in the environment may have adverse effects on the health of both human and animal populations.

In view of these considerations, it is vitally important to scrutinize carefully the probable avenues of contamination of the environment with 2,3,7,8-TCDD. It has been recognized for some time that 2,3,7,8-TCDD can be produced in the manufacture of 2,4,5-trichlorophenol. Other dioxins are similarly produced in the manufacture of other chlorophenols. The amounts of dioxins produced depend on process controls such as temperature and pressure. Since dioxins may be present in these and other manufactured chemical products, it is also likely that they may be present in the chemical wastes and sludges remaining from these processes. If this is the case, indiscriminate discharge of these wastes into the environment, or the use of improper disposal procedures could lead to the contamination of water, air, or foodstuffs. This might, in turn, result in widespread exposure of the population to TCDD's and other dioxins.

The report first presents an account of the chemistry of dioxins (Section 2), their physical and chemical properties and modes of formation. Section 3 considers the sources of dioxins, focusing on basic organic chemicals as well as on the chemical manufacture of chlorinated phenols and their derivatives.

Section 4 discusses the development of an analytical method for detecting dioxins in industrial wastes.

Section 5 provides a brief account of the major known incidents of human exposure to dioxins in the environment. In the aftermath of these incidents, which include both occupational exposures and exposures of the general public, scientists of many disciplines have undertaken extensive and continuing investigations of the fate of dioxins when they are released to the environment.

Section 6 reviews the current scientific knowledge of the health effects of dioxins, as indicated in epidemiological and laboratory studies of animal and human subjects who have been exposed to dioxin contamination. Section 7 reviews the known mechanisms of biodegradation, photodegradation, physical transport, and biological transport. The investigations indicate that the persistence of dioxins poses a serious environmental problem. In attempts to deal with this problem, numerous environmental research and development projects are aimed at developing methods of destroying these toxic contaminants after they have been formed. This work on dioxin disposal methods and decontamination procedures is described in Section 8.

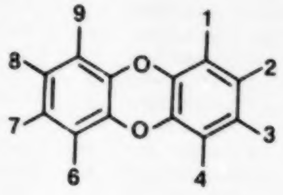
It is intended that this review of dioxin contaminants, from their formation through their dispersal into various environmental media and the consequent effects, can provide a point of perspective for those who are concerned with regulatory efforts and with research and development directed toward reducing the hazards of dioxin contamination.

SECTION 2

FORMATION OF DIBENZO-*P*-DIOXINS

CHEMISTRY OF DIOXIN FORMATION

A dioxin is any of a family of compounds known chemically as dibenzo-*p*-dioxins. Each of these compounds has as a nucleus a triple-ring structure consisting of two benzene rings interconnected to each other through a pair of oxygen atoms. Shown below are the structural formula of the dioxin nucleus and also the abbreviated structural convention used throughout the report.



Each of these substituent positions, numbered 1 through 4 and 6 through 9, can hold a chlorine or other halogen atom, an organic radical, or (if no other substituent is indicated in the formula or its chemical name) a hydrogen atom. The only differences in members of the dioxin family are in the nature and position of substituents.

Most environmental interest in dioxins and most studies of this family of compounds have centered on chlorinated dioxins, in which the chlorine atom occupies one or more of the eight positions. Theoretically, there are 75 different chlorinated dioxins, each with different physical and chemical properties, differing only in the number of chlorine atoms in each molecule and in their relative locations on the dioxin nucleus. There are, for example, two monochlorodioxins, in which one chlorine atom is attached to the nucleus at either position 1 or position 2. If two or more chlorine atoms are present, additional isomeric forms are possible, in accordance with the following schedule (Buser, Bosshardt, and Rappe 1978):

2 isomers of monochlorodibenzo-*p*-dioxin (MCDD's)
10 isomers of dichlorodibenzo-*p*-dioxin (DCDD's)
14 isomers of trichlorodibenzo-*p*-dioxin (Tri-CDD's)
22 isomers of tetrachlorodibenzo-*p*-dioxin (TCDD's)
14 isomers of pentachlorodibenzo-*p*-dioxin (Penta-CDD's)
10 isomers of hexachlorodibenzo-*p*-dioxin (Hexa-CDD's)
2 isomers of heptachlorodibenzo-*p*-dioxin (Hepta-CDD's)
1 octachlorodibenzo-*p*-dioxin (OCDD)

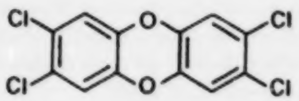
Table 1 lists the 75 possible chlorinated dioxins, and also notes the 40 that have been prepared and identified and whose analytical characteristics have been published (Buser, Bosshardt, and Rappe 1978; Buser 1975; Pohland and Yang 1972; Bolton 1978). Five others, as noted in the table, have been identified as distinct compounds but have not been clearly differentiated from each other (Buser, Bosshardt, and Rappe 1978; Buser 1975; Rappe 1978).

TABLE 1. CHLORINATED DIOXINS

1-chloro	a
2-chloro	a
1,2-dichloro	a
1,3-dichloro	a
1,4-dichloro	a
1,6-dichloro	a
1,7-dichloro	
1,8-dichloro	
1,9-dichloro	
2,3-dichloro	a
2,7-dichloro	a
2,8-dichloro	a
1,2,3-trichloro	a
1,2,4-trichloro	a
1,2,6-trichloro	
1,2,7-trichloro	
1,2,8-trichloro	
1,2,9-trichloro	
1,3,6-trichloro	
1,3,7-trichloro	a
1,3,8-trichloro	
1,3,9-trichloro	
1,4,6-trichloro	
1,4,7-trichloro	
2,3,6-trichloro	
2,3,7-trichloro	a
1,2,3,4-tetrachloro	a,d
1,2,3,6-tetrachloro	
1,2,3,7-tetrachloro	
1,2,3,8-tetrachloro	a
1,2,3,9-tetrachloro	
1,2,4,6-tetrachloro	
1,2,4,7-tetrachloro	
1,2,4,8-tetrachloro	
1,2,4,9-tetrachloro	
1,2,6,7-tetrachloro	a
1,2,6,8-tetrachloro	
1,2,6,9-tetrachloro	a
1,2,7,8-tetrachloro	a
1,2,7,9-tetrachloro	
1,2,8,9-tetrachloro	a
1,3,6,8-tetrachloro	a
1,3,6,9-tetrachloro	a
1,3,7,8-tetrachloro	a
1,3,7,9-tetrachloro	a
1,4,6,9-tetrachloro	a
1,4,7,8-tetrachloro	
2,3,7,8-tetrachloro	a
1,2,3,4,6-pentachloro	a
1,2,3,4,7-pentachloro	a
1,2,3,6,7-pentachloro	
1,2,3,6,8-pentachloro	c
1,2,3,6,9-pentachloro	
1,2,3,7,8-pentachloro	a
1,2,3,7,9-pentachloro	c
1,2,3,8,9-pentachloro	
1,2,4,6,7-pentachloro	
1,2,4,6,8-pentachloro	
1,2,4,6,9-pentachloro	
1,2,4,7,8-pentachloro	a
1,2,4,7,9-pentachloro	c
1,2,4,8,9-pentachloro	
1,2,3,4,6,7-hexachloro	a
1,2,3,4,6,8-hexachloro	a
1,2,3,4,6,9-hexachloro	a
1,2,3,4,7,8-hexachloro	a
1,2,3,6,7,8-hexachloro	a
1,2,3,6,7,9-hexachloro	a
1,2,3,6,8,9-hexachloro	b
1,2,3,7,8,9-hexachloro	a
1,2,4,6,7,9-hexachloro	a
1,2,4,6,8,9-hexachloro	b
1,2,3,4,6,7,8-heptachloro	a
1,2,3,4,6,7,9-heptachloro	a
Octachloro	a

a—Identified compounds.
b—One or the other of these compounds has been prepared.
c—A mixture of these three compounds has been prepared.
d—The Dow Chemical Company has recently reported the synthesis of all 22 TCDD isomers.

The interest of health and environmental researchers in dioxins arose principally because of the toxicity and distribution of one of these compounds, 2,3,7,8-TCDD, whose structural formula is as follows:



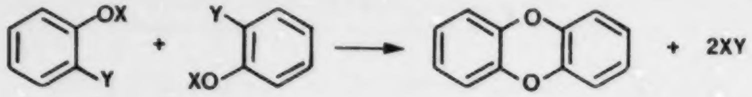
This is an unusual organic chemical, symmetrical across both horizontal and vertical axes. It is remarkable for its lack of reactive functional groups and its chemical stability (Poland and Kende 1976). It is an extremely lipophylic molecule, and only sparingly soluble in water and most organic liquids; it is a colorless crystalline solid at room temperature. The physical properties of 2,3,7,8-TCDD are shown in Table 2, along with those of OCDD, another chlorinated dioxin with twofold symmetry (World Health Organization 1977; Crummett and Stehl 1973).

TABLE 2. PHYSICAL PROPERTIES OF TWO CHLORINATED DIOXINS

		2,3,7,8-TCDD	OCDD
Empiric formula		$C_{12}H_4Cl_4O_2$	$C_{12}Cl_8O_2$
Percent by weight	C	44.7	31.3
	O	9.95	7.0
	H	1.25	
	Cl	44.1	61.7
Molecular weight		322	459.8
Melting point, °C		305	130
Decomposition temperature, °C		Above 700	Above 700
Solubilities, g/liter			
o-Dichlorobenzene		1.4	1.83
Chlorobenzene		0.72	
Anisole			1.73
Xylene			3.58
Benzene		0.57	
Chloroform		0.37	0.56
n-Octanol		0.048	
Methanol		0.01	
Acetone		0.11	
Dioxane			0.38
Water		0.0000002 (0.2 ppb)	

Dioxin Formation from Precursors

No published reports indicate that dioxins are formed biosynthetically by living organisms; these compounds apparently are not constituents of a normal growing environment. The presence of dioxins in fly ash, 2-chlorophenol, 2,4,6-trichlorophenol, and hexachlorobenzene indicates that there may be yet-undiscovered mechanisms that produce these compounds. In a recent study, chlorinated dioxins were created by pyrolysis of chlorobenzenes in the presence of air (Buser 1979b). Dioxins have been made from catechols in condensations with polychlorobenzenes and chloronitrobenzenes (World Health Organization 1977; Gray et al. 1976; March 1968). A pesticide manufacturer has reported the finding of chlorinated dioxins in cigarette smoke and fireplace soot (Dow Chemical Company 1978). Other possible routes of formation are examined in Section 3 of this report. One route that has been demonstrated by extensive chemical research is the formation of chlorinated dioxins from industrial chemicals, especially from certain "precursor" compounds that lead directly to dioxin formation. In generalized form, this reaction is as follows:



This reaction indicates that a compound may be a dioxin precursor if it meets two conditions:

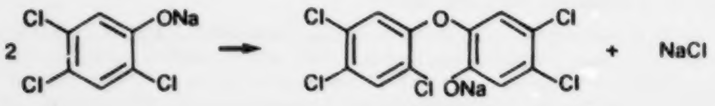
- The precursor compound must by an ortho-substituted benzene ring in which one of the substituents includes an oxygen atom directly attached to the ring.
- It must be possible for the two substituents, excluding the oxygen atom, to react with each other to form an independent compound.

These conditions are met by many organic compounds, including a class of mass-produced chemicals, the ortho-chlorinated phenols. The hydroxyl group of the phenol supplies the ring-attached oxygen atom. The hydrogen of the hydroxyl group is capable of reacting with chlorine, the other substituent, to form hydrogen chloride, an independent compound. An even more likely precursor is the sodium or potassium salt of an ortho-chlorinated phenol because the coproduct of this condensation is sodium or potassium chloride, either of which is an even more stable inorganic salt.

Almost all original dioxin researchers used ortho-chlorinated phenols as precursors. Most often, the reactions were conducted in the presence of sodium or potassium hydroxide, either of which will react spontaneously with the phenol groups to form the phenylate salts. Six chemical reactions, all of which have been performed in laboratory experiments, are shown in Figure 1 (Pohland and Yang 1972; World Health Organization 1977; Crosby, Moilanen, and Wong 1973; Milnes 1971).

Not all of these reactions, however, have produced the expected dioxin in high yield, and investigators have detected other dioxins and similar compounds that were not attributable to these simple reactions. Numerous studies have therefore explored the reaction mechanism of dioxin formation and the complex of competing reactions that create other compounds of this type (Buser 1975; Nilsson et al. 1974; Jensen and Renberg 1972; Plimmer 1973; Buser 1978).

The basic dioxin reaction actually occurs in two steps. In the condensation of 2,4,5-trichlorophenol, for example, one pair of substituents reacts first to form a phenoxyphenate, or substituted diphenyl ether, in accordance with the following reaction (Nilsson et al. 1974; Jensen and Renberg 1972; Buser 1978; Moore 1979).



PREDIOXIN

Compounds of this type have been termed "predioxins." They have been identified in waste sludges and commercial products as well as in the products of laboratory experiments (Jensen and Renberg 1972; Arsenault 1976; Jensen and Renberg 1973).

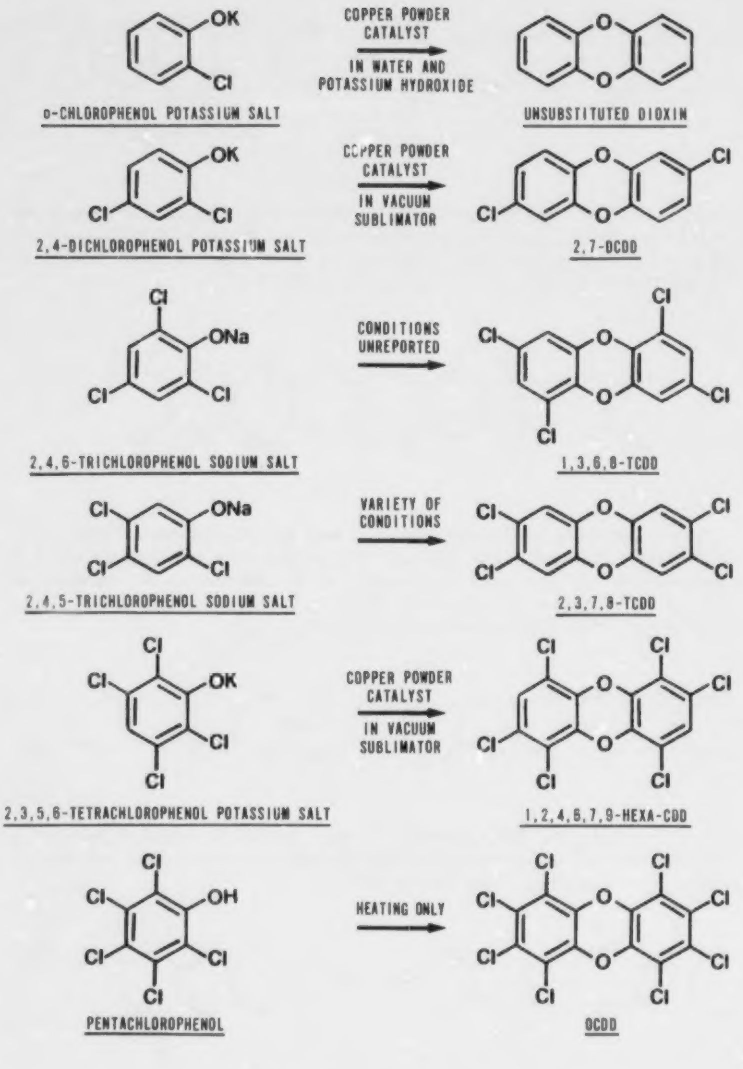
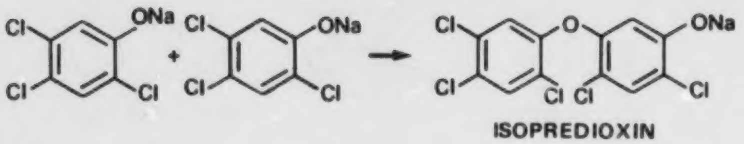
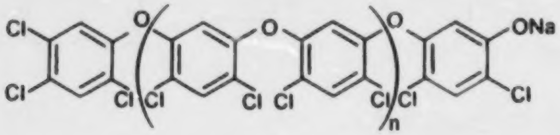


Figure 1. Formation of dioxins.

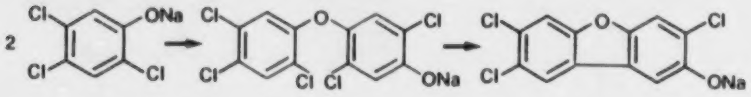
There are other competing reactions, however. With some precursor compounds, condensation may occur with a chlorine atom that is not in the ortho position to a hydroxyl group. One study suggests that a meta chlorine will be favored, in accordance with the following reaction (Langer, Brady, and Briggs 1973).



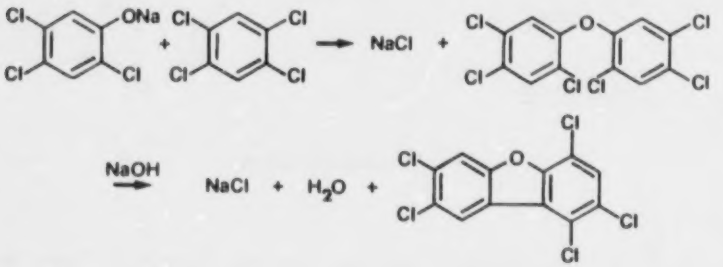
The end product has been termed an "isopredioxin" (Jensen and Renberg 1973). To this isopredioxin, additional molecules of sodium-2,4,5-trichlorophenate may attach, creating a polymerized compound of three, four, or more monomers (Langer, Brady, and Briggs 1973; Langer et al. 1973).



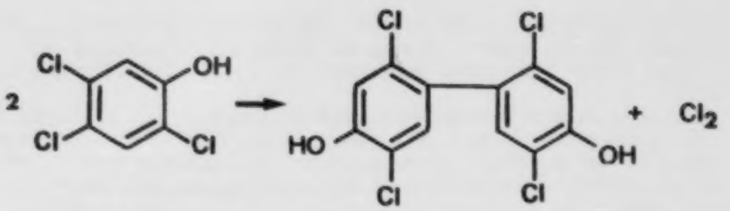
Investigators have noted similar reactions with para chlorine atoms, which form another type of isopredioxin. Either of the isopredioxins may polymerize into longer chains, or they may lead with loss of chlorine to the creation of dibenzofurans (Jensen and Renberg 1972; Langer, Brady, and Briggs 1973; Deinzer et al. 1979; Chemical Engineering 1978).



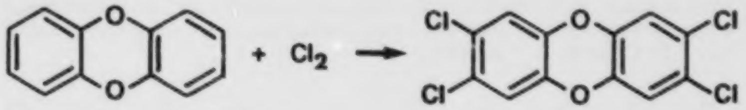
It is believed that dibenzofurans are also formed by reaction between a chlorophenol and a polychlorobenzene through an intermediate creation of another type of diphenyl ether (Buser 1978).



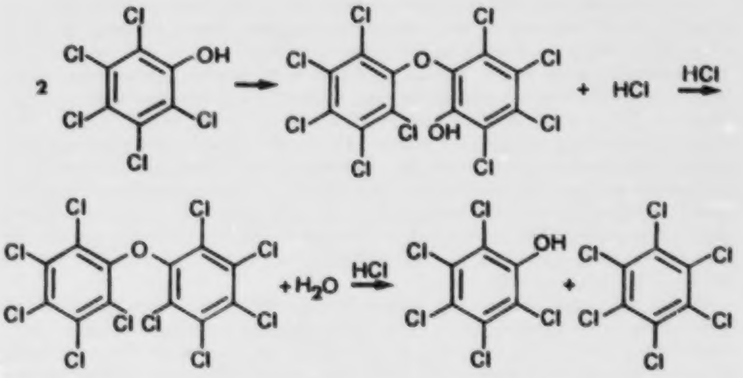
Another competing reaction that involves loss of chlorine is the reaction to form dihydroxy chlorinated biphenyls (Jensen and Renberg 1973).



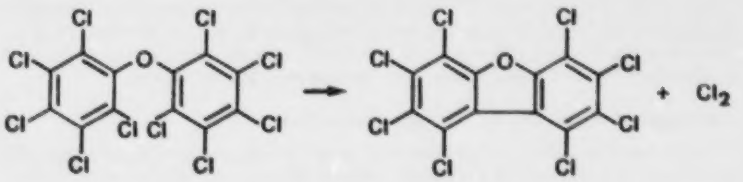
The chlorine thus released may react with other rings to form compounds with higher chlorine saturation. Preparation of 2,3,7,8-TCDD was accomplished by treatment of unsubstituted dioxin (World Health Organization 1977).



Other competing reactions have been described for pentachlorophenol, which has been shown to degenerate, when heated, into hexachlorobenzene and water by a reaction sequence that includes an intermediate decachlorodiphenylether (Plimmer 1973).



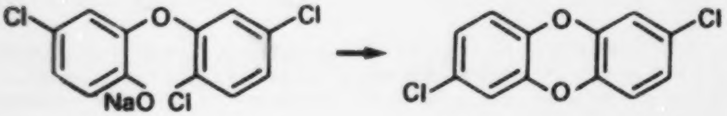
Alternatively, the predioxin or the decachlorodiphenylether may lose chlorine through reactions with water to form hexachloro or heptachlorodioxins or to form octa- and nonachlorodiphenylethers. Loss of chlorine may also create octachlorodibenzofuran in accordance with the following reaction (Crosby, Moilanen, and Wong 1973; Jensen and Renberg 1973).



These competing reactions are predominant only with acidic pentachlorophenol, however. Heating the sodium salt of pentachlorophenol produces OCDD in essentially quantitative yield (World Health Organization 1977).

Except for pentachlorophenol, once a predioxin is formed, there are apparently no competing reactions other than its reversal into the precursor. In one test, when Irgasan DP-300, a predioxin (see Section 3, p. 111), was heated to 980°C, only two classes of compounds were created: dioxins and precursor molecules (Nilsson et al. 1974).

The competing reactions clearly indicate why dioxins generally are formed only in trace quantities and why they appear in a complex mixture with polymers and other multiring structures, many of which are also toxic. It has been more difficult to explain why dioxins other than the one predicted by theory are also found in these mixtures. In the laboratory, for example, a predioxin for 2,8-DCDD created a small amount of this dioxin when heated; however, the principal dioxin formed was 2,7-DCDD (Boer et al. 1971).



It was originally believed that such unexpected dioxins were created by arbitrary transfers of chlorine that occurred within the energetic predioxin molecules (Boer et al. 1971). More recent work has demonstrated that a long-recognized chemical phenomenon known as the "Smiles rearrangement" is often operational during dioxin creation, in which one of the rings spontaneously reverses into its mirror image at the instant of ring closure (Gray et al. 1976; March 1968). This rearrangement fully explains the reaction shown above, and researchers can now predict with some certainty which dioxins will be formed from specific precursors or predioxins. Even this development has not satisfied all observational evidence, however, especially with the more highly chlorinated dioxins. Some researchers believe that an equilibrium process is at work, in which dioxins slowly lose or gain chlorine atoms to approach the most stable mixture of compounds (Rawls 1979; Miller 1979; Ciaccio 1979).

Predioxin formation does not ensure dioxin formation (Jensen and Renberg 1972; Jensen and Renberg 1973). Pentachlorophenol attains equilibrium with its precursor in a reversible reaction but forms large amounts of dioxins only in the presence of an alkali (Langer et al. 1973). Irgasan DP-300 can be chlorinated and otherwise modified chemically without inducing ring closure (Nilsson et al. 1974; Yang and Pohland 1973). "High amounts" of predioxins have been found in commercial products in which no dioxin could be detected. Another study revealed predioxin concentrations as much as 20 times greater than dioxin concentrations (Jensen and Renberg 1972). In still another study, the concentration of hydroxypolychlorodiphenyl ethers (predioxins plus isopredioxins) was more than 50 times the dioxin concentration (Deinzer et al. 1979 ; Chemical Engineering 1978). Although not specifically noted in published literature, predioxin formation appears to be more likely than dioxin formation. It is possible that steric or electronic hindrances interfere with the final step of ring closure, and that predioxins may be formed under less-rigorous reaction conditions.

Minimum Conditions for Dioxin Formation

Since dioxins usually are formed only in low yields, the minimum conditions leading to their formation are poorly defined. Heat, pressure, photostimulation, and catalytic action have all been shown to encourage the reactions from chlorinated precursors to predioxins and then to dioxins.

The temperature required for dioxin formation is variously reported at values from 180° C to 400° C (Milnes 1971; Langer, Brady, and Briggs 1973; Crossland and Shea 1973; Gribble 1974; Buser 1978). As previously noted, sodium pentachlorophenate is converted to essentially pure OCDD at approximately 360° C (Langer et al. 1973). The same series of tests indicated decomposition of several other chlorinated dioxin precursors at temperatures from about 310° to 370° C, with formation of varying quantities of dioxins (Langer et al. 1973). Essentially quantitative formation of many different dioxins from chlorinated catechols and *o*-chloronitrobenzenes has been achieved at 180° C (Gray et al. 1976; March 1968). Direct combustion of herbicides or impregnated sawdust can create dioxins (Nilsson et al. 1974; Langer, Brady, and Briggs 1973; Stehl and Lamparski 1977; Ahling and Lindskog 1977; Jansson, Sundstrom, and Ahling 1978), especially if there is a deficiency of oxygen (Chem. and Eng. News 1978), but the temperature of formation under these conditions cannot be measured (this phenomenon may be limited to formation of dioxins from pentachlorophenol; reports are indefinite). Apparently no definitive study has determined the temperature of formation of 2,3,7,8-TCDD.

Pressure is needed to retain some precursor compounds in the liquid state to permit dioxin formation (Jensen and Renberg 1972). At atmospheric pressure, the boiling point of many precursors is apparently lower than the temperature needed to form dioxins, and therefore the precursors escape from the reaction vessel before decomposition reactions can occur.

Irradiation of pentachlorophenol with ultraviolet light has caused the formation of OCDD (World Health Organization 1977; Crosby, Moilanen, and Wong 1973; Plimmer et al. 1973; Crosby and Wong 1976). Irradiation of 2,4-dichlorophenol, however, energized the hydrogen atom at position 6 of one ring and created a predioxin as a principal product, but ring closure apparently did not occur (Plimmer et al. 1973). This experiment also produced a dihydroxy biphenyl, probably through the competing reaction described previously. It has been postulated that although dichloro, trichloro, and tetrachloro dioxins may be formed by irradiation, they do not accumulate because they decompose rapidly by the same mechanism (Crosby, Moilanen, and Wong 1973). As outlined in Section 5, the less-chlorinated dioxins are unstable when exposed to ultraviolet light.

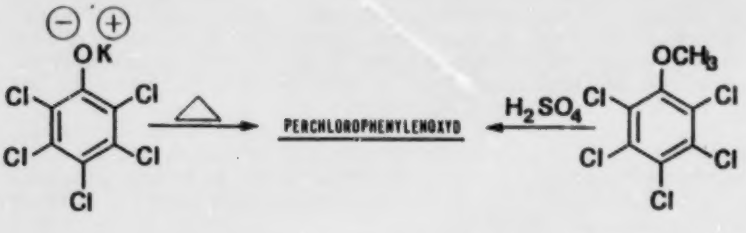
In laboratory production of dioxins, catalysts have been used to increase reaction rates and reaction yields. Powdered copper, iron or aluminum salts, and free iodine have been used (Pohland and Yang 1972; World Health Organization 1977), and all of these are known to stimulate many reactions of chlorinated organic compounds (Wertheim 1939). One report indicates that heavy metallic ions may decrease decomposition temperature (Langer et al. 1973). Presence of heavy metals may, however, only encourage competing reactions; the silver salt of pentachlorophenol, for example, decomposes at about 200° C to yield polymerized materials but no dioxins (Langer et al. 1973).

Formation of dioxins is an exothermic reaction (Langer et al. 1973) that releases heat as the molecules contract into a more compact arrangement. No published data define the amount of heat created by formation of the various dioxins.

Once formed, the dioxin nucleus is quite stable. Laboratory tests have shown that it is not decomposed by heat or oxidation in a 700° C incinerator, but pure compounds are largely decomposed at 800° C (Ton That et al. 1973). A recent report states that the nucleus survives intact through incineration up to 1150° C (Crummett of Dow Chemical Company indicates temperature should be 1050° C) if it is bound to particulate matter (Rawls 1979; Miller 1979; Ciaccio 1979). Chlorinated dioxins lose chlorine atoms on exposure to sunlight or to some types of gamma radiation, but the basic dioxin structure is largely unaffected (Crosby et al. 1971; Buser, Bosshardt, and Rappe 1978). In comparison with almost any other organic compound, the biological degradation rate of chlorinated dioxins is slow, although measured rates differ widely (Zedda, Cirla, and Sala 1976; Commoner and Scott 1976b; Matsumura and Benezet 1973; Huetter 1980).

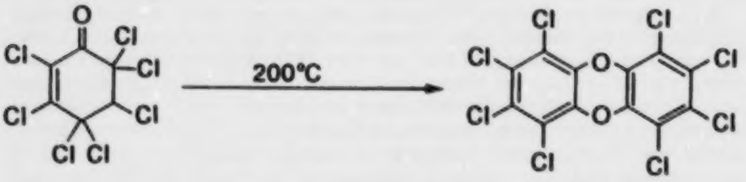
LABORATORY PREPARATIONS OF DIOXINS

The first report of intentional preparation* of this class of compounds occurred in 1872, when Merz and Weith described the preparation of "perchlorophenylenoxyd" by thermolysis of potassium pentachlorophenate (1). Hugounenq (1890) reported that the treatment of pentachloroanisole (2) with concentrated sulfuric acid also gives "perchlorophenylenoxyd."



1 2

Soon after these reports, Zinke (1894) and Blitz (1904) showed that heating heptachlorohexenone (3) to 200° C gave "perchlorophenylenoxyd." Not until 1960 was it shown that "perchlorophenylenoxyd" is octachlorodibenzo-*p*-dioxin (OCDD) (4) (Denivelle 1960).



3 4

The mechanism of the reactions reported by Zinke and Blitz remained unknown for over half a century. In 1961 Kulka showed that heptachlorocyclohexenone (3) eliminates a molecule of hydrogen chloride at about 180° C to give hexachlorocyclohexadienone (5). Kulka proposed that this compound, on heating to 200° C, loses a chlorine radical to give the pentachlorocyclohexadienone radical (6) (or its resonance isomer, the pentachlorophenoxy radical (7)), which then dimerizes to give (4) and a molecule of chlorine.

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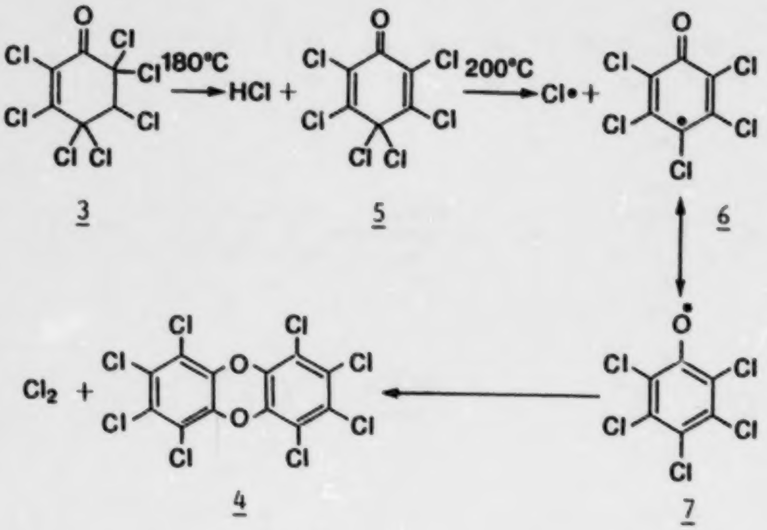
*According to scientists of Dow Chemical Company (Rawls 1979), dioxins have been prepared since "Prometheus stole fire from the gods and brought it to mankind."



The mechanism that Kulka proposed, supplemented with earlier work by Denivelle (1959, 1960), initiated numerous reports on the preparation of halogenated dibenzo-*p*-dioxins under neutral or acidic conditions. A number of these reactions are listed in Table 3.

Bayer (1903) patented a process for the preparation of dibenzo-*p*-dioxin (8) from sodium *o*-chlorophenylate (9). This procedure, which is an extension of the earlier work reported by Merz and Weith (1872), is based on Ullmann's preparation of diphenylamines (Ullmann 1903) and is generally referred to as a modified Ullmann condensation (Aniline 1973). Although the yields of the modified Ullmann reaction rarely exceed 30 percent, this procedure was standard for the preparation of both substituted and unsubstituted dioxins until the early 1970's. Examples of the utilization of this process are given in Table 4, showing minor as well as major products of reaction, where applicable.

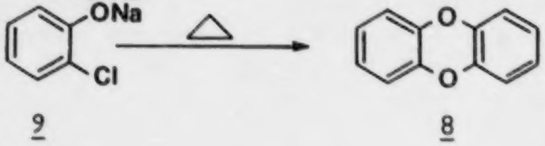
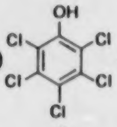
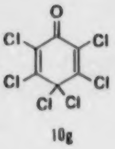
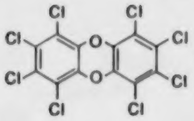
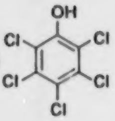
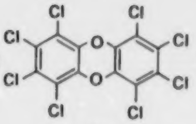
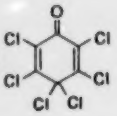
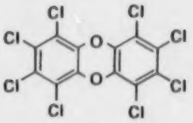
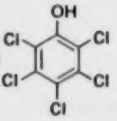
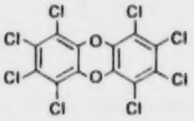
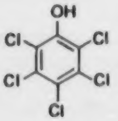
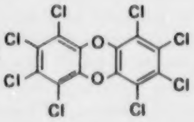
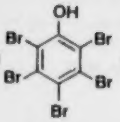
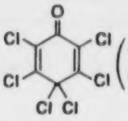
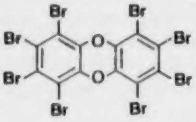
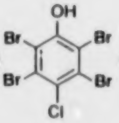
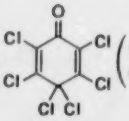
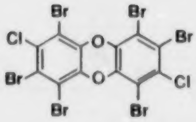
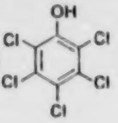
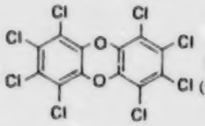
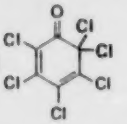
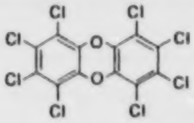
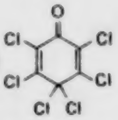
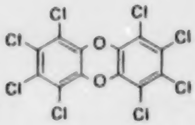
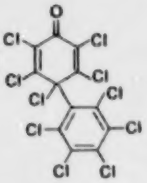
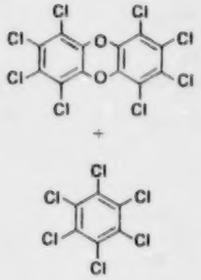
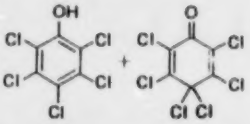
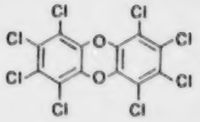
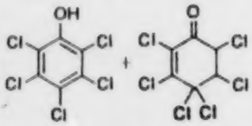
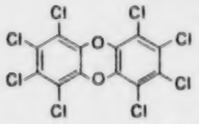


TABLE 3. PERHALO DIBENZO-*p*-DIOXINS VIA FREE RADICAL REACTIONS

Item	Reactant	Conditions	Product	(Yield)[a]	Ref.
①	 40g +  10g	250°-300°C 25min		(83%)	b
②	 25g + Cl_2	REFLUXING 1,2,4 TRICHLOROBENZENE 16h	 18g	(83%)	c
③		270°-280°C 30min	 11g	(73%)	c
④	 25g + Br_2	1,2,4 TRICHLOROBENZENE REFLUX 16h		(52%)	c
	 + I_2	1,2,4 TRICHLOROBENZENE REFLUX 16h		(23%)	c
⑤	 35g +  0.2g (or Cl_2 or Br_2)	320°-360°C 35min		(52%) (15g)	c
⑥	 30g +  0.2g (or Cl_2 or Br_2)	300°-350°C 30min		(62%) (15g)	c

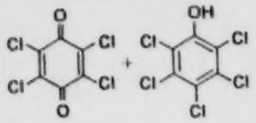
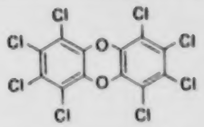
(continued)

TABLE 3 (continued)

Item	Reactant	Conditions	Product	(Yield)[a]	Ref.
⑦		300°C		 (4%) (POOR)	d e f
⑧		260°C			d
⑨		260°C			d
⑩		260-280°C			d
⑪	 200g + 75g	120-200°C		(84%)	g
⑫	 222g + 82g	120-200°C		(80%)	g

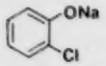
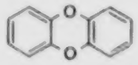
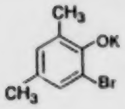
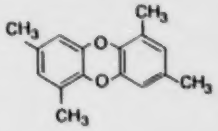
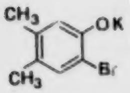
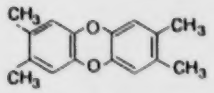
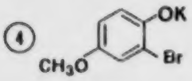
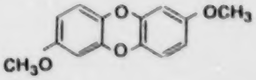
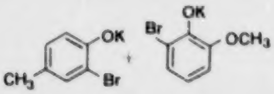
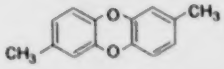
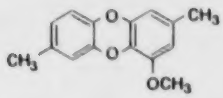
(continued)

TABLE 3 (continued)

Item	Reactant	Conditions	Product	(Yield)[a] Ref.
⑬		270°C IN QUINOLINE		d

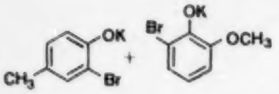
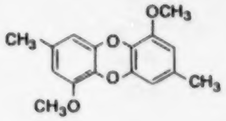
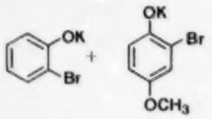
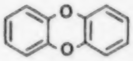
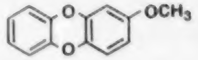
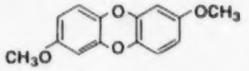
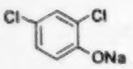
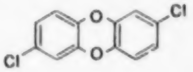
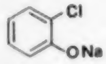
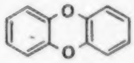
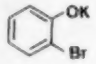
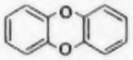
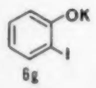
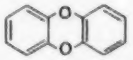
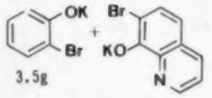
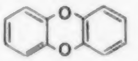
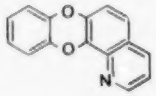
a—If no yield is stated, no value is reported in reference.
b—Kulka 1965.
c—Kulka 1961.
d—Denivelle, Fort, and Pham 1959.
e—Gribble 1974.
f—Sandermann, Stockmann, and Casten 1957.
g—Kaupp and Klug 1962.

TABLE 4. ULLMANN CONDENSATION REACTIONS

Item	Reactant	Conditions	Product	(Yield)[a] Ref.
①		220°, 10h		(25%) b
②		190-200°C Cu, Cu(OAc)$_2$		c
③		190-200°C Cu, Cu(OAc)$_2$		c
④		190-200°C Cu, Cu(OAc)$_2$		c
⑤			 	d

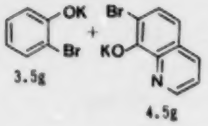
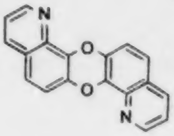
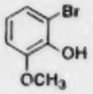
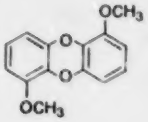
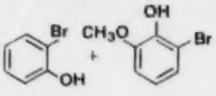
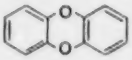
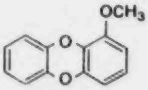
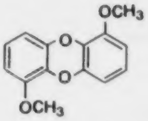
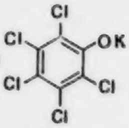
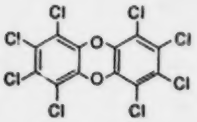
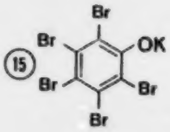
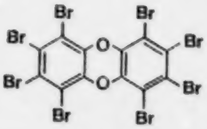
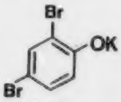
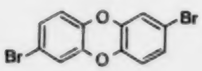
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a Ref.
⑤				
⑥			  	d
⑦		160°C Cu 1h		e
⑧		150°C Cu 1h		f
⑨		160°-220°C Cu, 110min		(50%) f
⑩	 6g	200°C, Cu 3h		(0.2g) g
⑪	 3.5g 4.5g	190°C Cu 2h	 	(0.09g) h,i (0.08g)

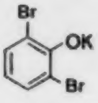
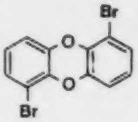
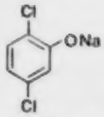
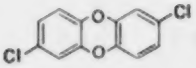
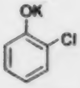
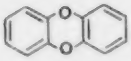
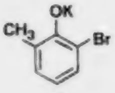
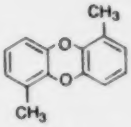
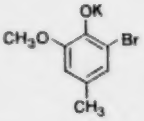
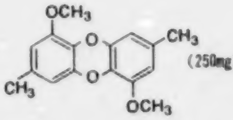
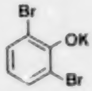
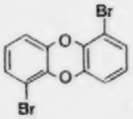
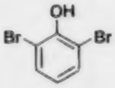
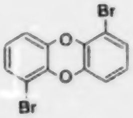
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a	Ref.
⑪	 3.5g 4.5g	190°C Cu 2h		(TRACE)	
⑫		180°C 30min			g
⑬	 5.78g 8.58g	180°C KOH, Cu 30min		(0.164g)	j
				(0.287g)	
				(0.132g)	
⑭	 3.25g	200°C Cu 2h		(20mg)	k
⑮	 3.15g	200°C Cu 2h		(40mg)	k
⑯	 3.25g	185°C Cu 1.5h		(40mg)	k

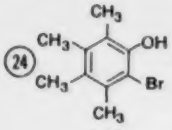
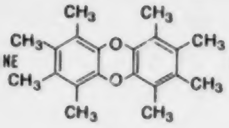
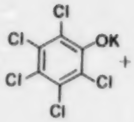
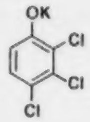
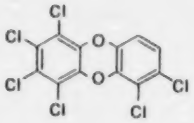
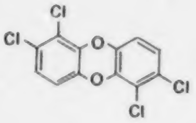
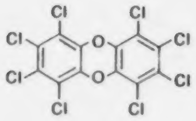
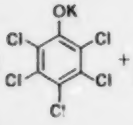
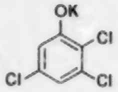
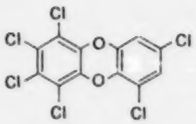
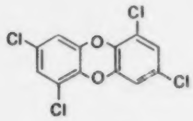
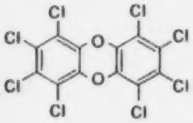
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a	Ref.
⑰	 1.75g	180°C Cu 1.5h		(40mg)	k
⑱	 3.7g	210°C 0.3g Cu 3h		(0.9g)	l
⑲		190°C Cu 4h		(25%)	l
⑳	 2g	195°C Cu POWDER 30min		(60 mg)	m
㉑	 10g	200°C Cu POWDER, 1.5h		(250mg)	m
㉒	 6g	190°C Cu POWDER 1h		(3.1g)	n
㉓	 1g	145°C Cu POWDER, PYRIDINE 2.5h		(10mg)	n

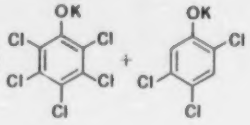
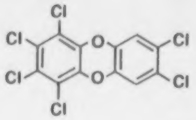
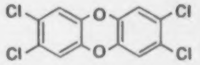
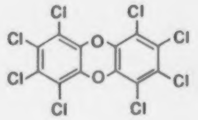
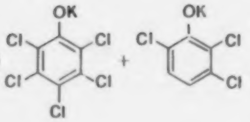
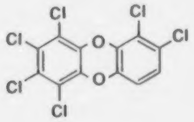
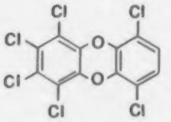
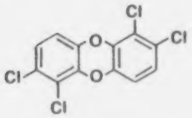
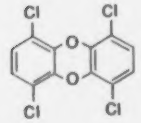
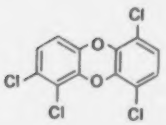
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a	Ref.
㉔	 1.17g	145°C Cu POWDER, PYRIDINE 3h		(8mg)	o
㉕	 + 	290°C 1-4h			p
					
					
㉖	 + 	290°C 1-4h			p
					
					

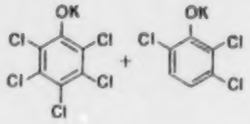
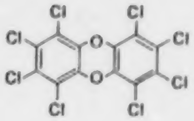
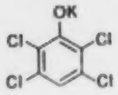
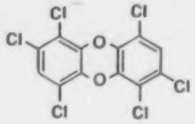
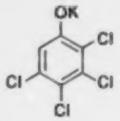
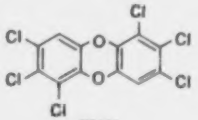
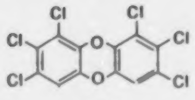
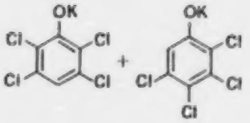
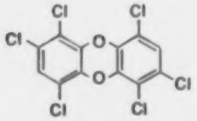
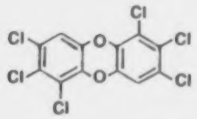
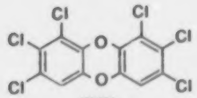
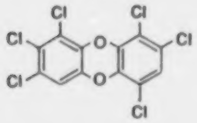
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a Ref.
㉗		290°C 1-4h		p
				
				
㉘		290°C 1-4h		p
				
				
				
				

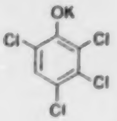
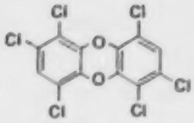
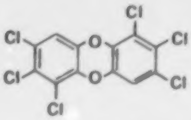
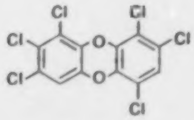
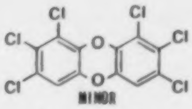
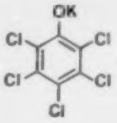
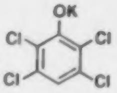
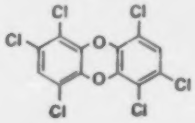
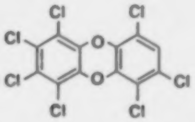
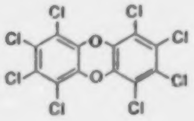
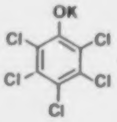
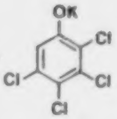
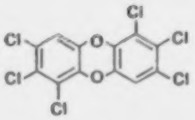
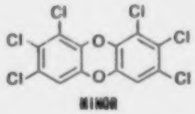
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a Ref.
㉘		290°C 1-4h		
㉙		290°C 1-4h		p
㉚		290°C 1-4h	 MAJOR  MINOR	p
㉛		290°C 1-4h	   MINOR 	p

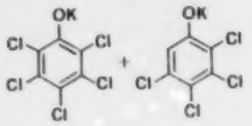
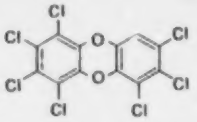
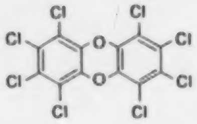
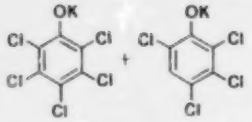
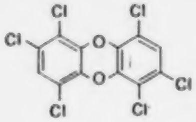
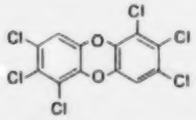
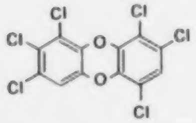
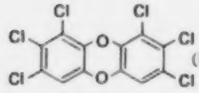
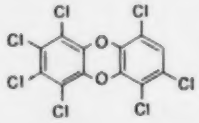
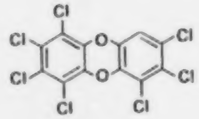
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a Ref.
㉜		290°C 1-4h	    MINOR	p
㉝	 + 	2[illegible]°C 1-4h	  	p
㉞	 + 	290°C 1-4h	  MINOR	p

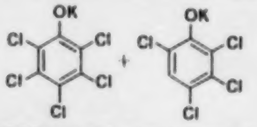
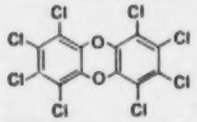
(continued)

TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)^a Ref.
㉞		290°C 1-4h		
				
㉟		290°C 1-4h		p
				
				
			 (MINOR)	
				
				

(continued)

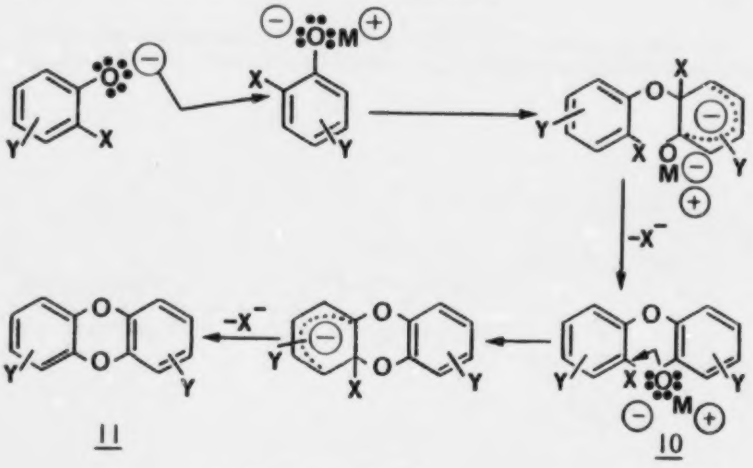
TABLE 4 (continued)

Item	Reactant	Conditions	Product	(Yield)[a] Ref.
㉟		290°C 1-4h		

a—If no yield is stated, no value is reported in reference.
b—Cullinane and Davies 1936.
c—Tomita 1933.
d—Tomita and Tani 1942
e—Julia and Baillargc 1953
f—Tomita, Nakano, and Hirai 1954.
g—Tomita and Yagi 1958.
h—Fujita and Gota 1955.
i—Fujita et al. 1956.
j—Inubushi et al. 1959.
k—Tomita, Ueda, and Narisada 1959.
l—Deniveile, Fort, and Hai 1960.
m—Ueda 1962.
n—Ueda and Akio 1963.
o—Ueda 1962.
p—Buser 1975.

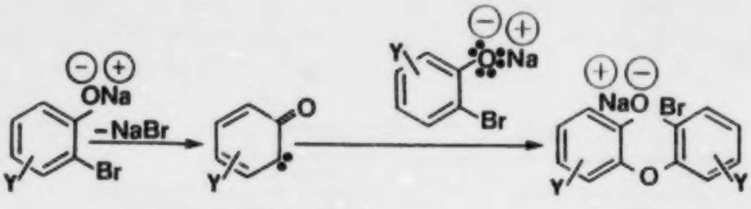
As the reactions in Table 4 show, dioxins have been formed from the alkali metal salts of ortho-halophenols through pyrolysis at temperatures of 200° to 300° C for several hours, usually in the presence of copper powder or copper salts. Entries 23 and 24 in Table 4 show that much milder conditions (pyridine as the base and a temperature of only 145° C for 2 to 3 hours) can give significant concentrations of dibenzo-*p*-dioxins (Ueda 1963).

The mechanism for this type of reaction was generally believed to involve a nucleophilic attack of the phenoxy ion on a second phenolate ring (Buser 1975), followed by expulsion of the halide to give the *o*-halophenoxyphenate (10) (predioxin). An intramolecular nucleophilic aromatic substitution followed by expulsion of a halide gives the dibenzo-*p*-dioxin (11).



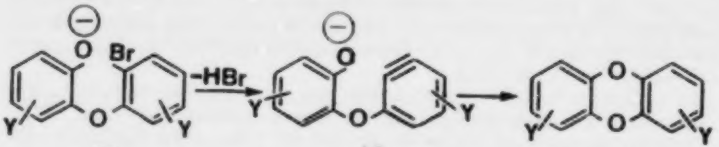
X=leaving group
(e.g. Cl, F, Br, I, NO_2, SO_3R)
M=alkali metal cation
Y=any substituent group

In 1974 Cadogan, Sharp, and Trattles proposed a more reasonable mechanism involving the α-ketocarbene (12), which is attacked by the phenoxide to give (10).



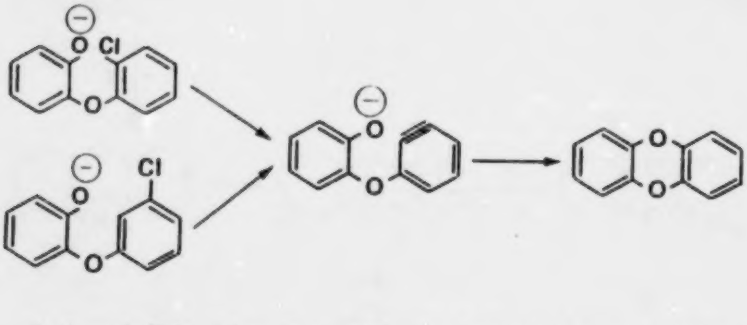
12 10

They also proposed that the conversion of the o-halophenoxyphenate to dibenzo-p-dioxin occurs via a benzyne intermediate (13).

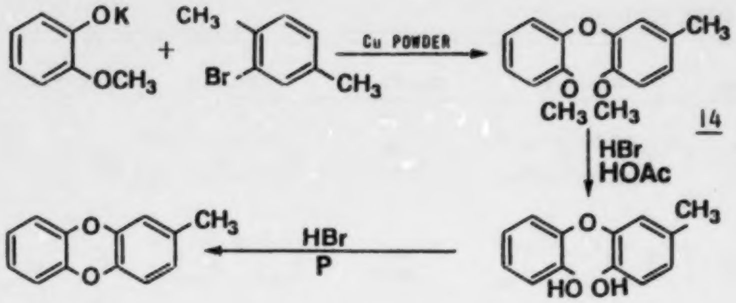


10 13 11

The evidence in favor of this mechanism is quite convincing since both ortho- and meta-halophenoxyphenates are converted to the same dibenzodioxin, as shown below.



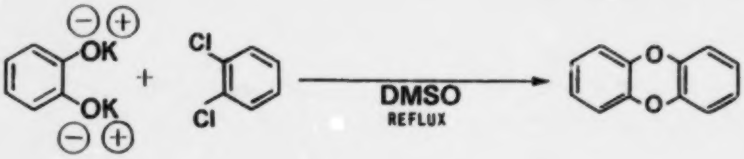
As shown in Table 4 (items 5, 6, 11, 13, 25–28, and 31–35), complex mixtures result from attempts to prepare unsymmetrical dibenzo-p-dioxins using the modified Ullmann reaction. An early attempt to circumvent this problem involved the synthesis of a protected form of the unsymmetrical predioxin intermediate (14) (Tomita 1938) followed by its conversion to the dioxin in a separate procedure as shown on the next page (Tomita 1938; Keimatsu 1936).



14

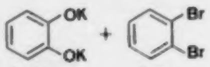
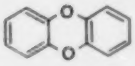
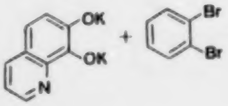
This procedure has the advantage of giving a single dibenzo-*p*-dioxin isomer; however, it is limited in that yields of the dioxin rarely exceed 10 percent (Tomita 1938).

A newer and more general procedure for the preparation of unsymmetrical (as well as symmetrical) dibenzo-*p*-dioxins involves the reaction of catechol salts with ortho-dihalobenzenes in dimethylsulfoxide (DMSO) (Pohland 1972; Kende 1974).



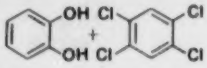
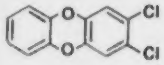
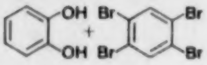
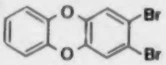
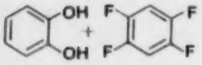
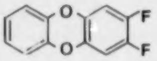
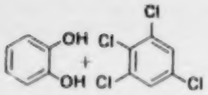
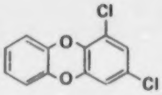
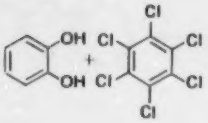
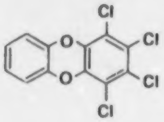
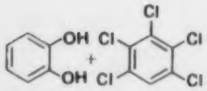
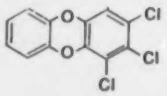
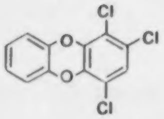
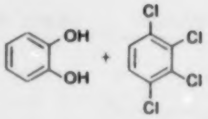
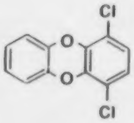
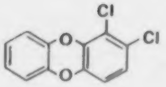
This procedure is a modification of a much earlier approach to the synthesis of dibenzo-*p*-dioxin, which suffered low yields (Tomita 1932) or no dioxin formation (Fujita 1955). The improved process gives very high yields of dibenzo-*p*-dioxins when dimethylsulfoxide is used as the solvent. Whether this result is simply a solvent effect or DMSO plays a chemical role in the reaction has not been determined. Examples of the utilization of this reaction for the preparation of dibenzo-*p*-dioxins are included in Table 5.

TABLE 5. CATECHOL-BASED REACTIONS

Item	Reactant	Conditions	Product	(Yield)[a] Ref.
①	 7.75g + 5.9g	200°C Cu POWDER $CuNO_3$ 3h		b
②		190°C Cu POWDER 2h	(NO REACTION)	c

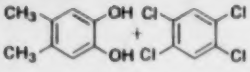
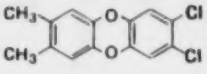
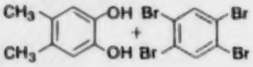
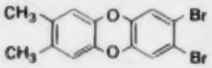
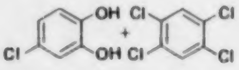
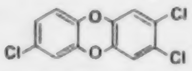
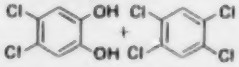
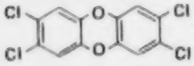
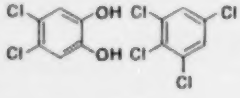
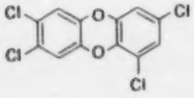
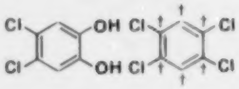
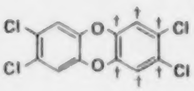
(continued)

TABLE 5 (continued)

Item	Reactant	Conditions	Product	(Yield)[a]	Ref.
③		KOH DMSO, △		(81%)	d
④		KOH DMSO, △		(25%)	e
⑤		KOH DMSO, △		(41%)	e
⑥		KOH DMSO, △		(31%)	e
⑦		KOH DMSO, △		(41%)	e
⑧		KOH DMSO, △	 + 	(35% TOTAL)	e
⑨		KOH DMSO, △	 + 	(40% TOTAL)	e

(continued)

TABLE 5 (continued)

Item	Reactant	Conditions	Product	(Yield)[a]	Ref.
⑩		KOH DMSO, △		(49%)	e
⑪		KOH DMSO, △			e
⑫		KOH DMSO, △		(50%)	e
⑬		KOH DMSO, △		(19%)	e
⑭		KOH DMSO, △		(40%)	e
⑮		KOH DMSO, △		‡	f

†—Evenly distributed carbons.

‡—Preparation of uniformly labelled ^{14}C TCDD isomers (148 millicurie/millimole)

a—If no yield is stated, no value is reported in reference.

b—Tomita 1932.

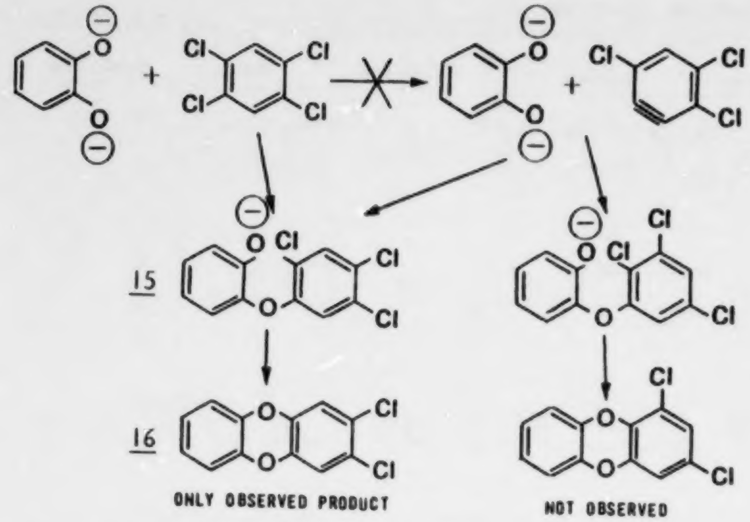
c—Fujita and Gota 1955.

d—Pohland and Yang 1972.

e—Kende et al. 1974.

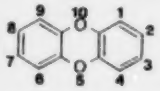
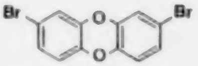
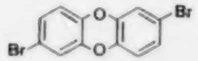
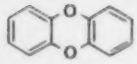
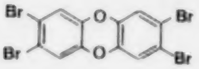
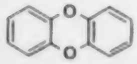
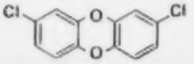
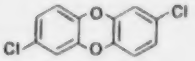
f—Rose et al. 1976.

Although no mechanistic studies of this reaction have been reported, it is clear that the initial attack of the catechol dianion on the polyhalobenzene does not occur via a benzene intermediate, since in item 3 of Table 5 one would expect two different dioxins, which is not the result. This does not preclude the possibility that a benzyne intermediate is involved in the conversion of the predioxin (15) to the 2,3-dichlorodibenzo-*p*-dioxin (16), as has been proposed for similar predioxin cyclizations (Cadogan 1974).



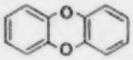
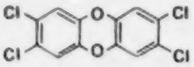
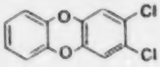
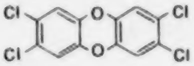
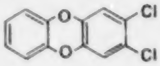
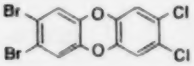
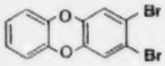
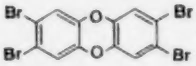
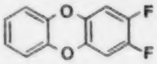
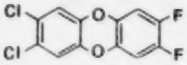
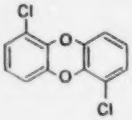
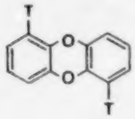
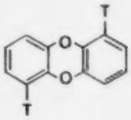
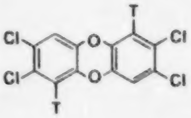
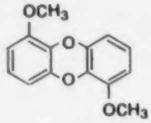
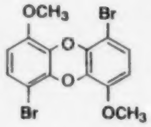
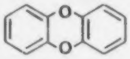
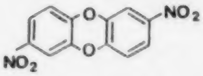
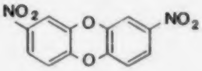
Numerous approaches to the preparation of substituted dioxins are based on elaboration of the dibenzo-*p*-dioxin skeleton via electrophilic aromatic substitution reactions. These applications are summarized in Table 6.

TABLE 6. SUBSTITUTION REACTIONS

Item	Reactant		Conditions	Product	(Yield)[a] Ref.
①		+ Br_2		 	b
②		+ Br_2	$Fe(Br)_3$, CAT.		b
③		+ Cl_2		 	b

(continued)

TABLE 6 (continued)

Item	Reactant		Conditions	Product	(Yield)[a]	Ref.
④		+ Cl_2	$Fe(Cl)_3$	 + PENTA-CDD AND TRI-CDD	(LOW)	b
⑤		+ Cl_2			(41%)	c
⑥		+ Br_2			(76%)	c
⑦		+ Br_2			(87%)	c
⑧		+ Cl_2			(24%)	c
⑨		+ TRITIUM	CAT			d
⑩		+ Cl_2	$FeCl_3, I_2$(CAT)			d
⑪		+ Br_2			(90%)	e
⑫			HNO_3, △			f
						f

(continued)

TABLE 6 (continued)

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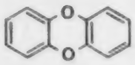
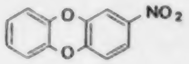
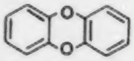
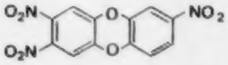
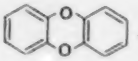
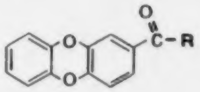
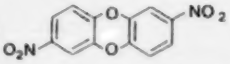
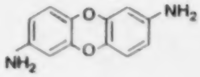
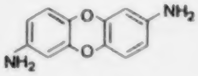
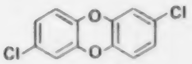
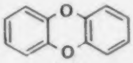
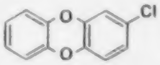
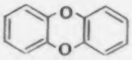
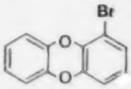
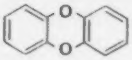
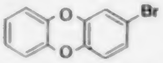
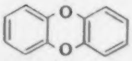
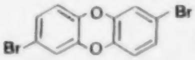
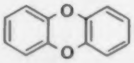
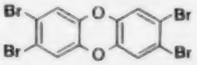
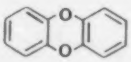
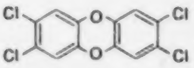
⑬		HNO_3 HOAc, 0°C			f
		HNO_3, Δ			
⑭	 + RCOCl	$AlCl_3$			g
⑮		H_2/Pd			h
⑯		HONO, CuCl			h
⑰	 4.6g	Cl_2, HOAc		(1g)	i,j
⑱	 9.2g	1. PHENYLLITHIUM 2. Br_2		(1g)	i,j
⑲		KBr $KBrO_3$, HOAc, 120°C		(40%)	i,j
⑳	 4.6g	Br_2, HOAc, 120°C		(0.6g)	i,j
㉑		Br_2, HOAc, 120°C			i,j
㉒	 26g	Cl_2, $FeCl_3$, I_2		(20g)	k

(continued)

TABLE 6 (continued)

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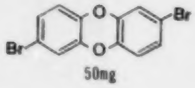
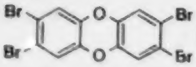
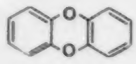
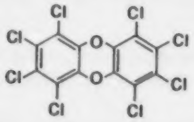
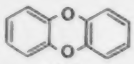
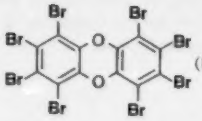
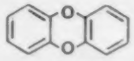
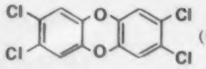
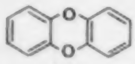
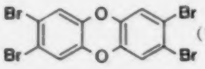
㉓	 50mg	Br_2, HOAc		(60mg)	l
㉔		Cl_2, $FeCl_3$, I_2			l
㉕	 0.5g	Br_2		(0.7g)	m
㉖	 0.2g	Cl_2		(0.1g)	m
㉗	 0.5g	Br_2		(1.54g)	m

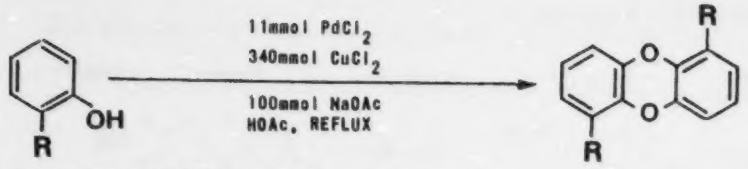
a—If no value is stated, no value is reported in reference.
b—Gilman and Dietrich 1957.
c—Kende et al. 1974.
d—Vinopal, Yamamoto, and Casida 1973.
e—Ueda 1963.
f—Tomita 1935.
g—Tomita 1937.
h—Ueo 1941.
i—Gilman and Dietrich 1957.
j—Gilman and Dietrich 1958.
k—Sandermann, Stockmann, and Casten 1957.
l—Tomita, Ueda, and Narisada 1959.
m—Denivelle, Fort, and Hai 1960.

As indicated in Table 6, electrophilic aromatic substitution occurs first at position 2. (The dioxin numbering sequence is shown in item 1.) If the newly introduced substituent is deactivating (halogen or nitro), the next attack occurs at either position 7 or 8. Gilman (1957, 1958) found that position 1 can be metalated by treatment of dibenzo-*p*-dioxin with alkyl or phenyllithium reagents allowing this position to be substituted.

Miscellaneous Dioxin Preparations

Buser (1976) has developed a method for the preparation of qualitative standards of polychlorinated dioxins based on the photodechlorination of octachlorodioxin (Crosby 1971, 1973). Irradiation of octachlorodibenzo-*p*-dioxin yields a mixture of tri-, tetra-, penta-, hexa-, and heptachlorodibenzo-*p*-dioxin that is useful for the analysis of materials suspected to contain polychlorodioxins.

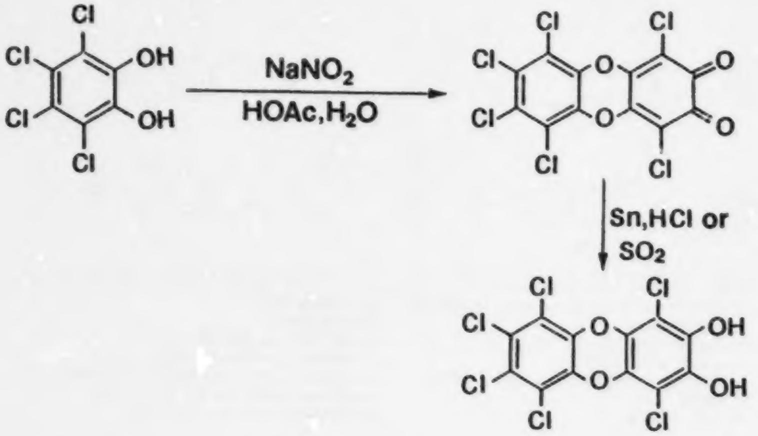
Lester and Brennan (1972) have patented a process for the direct conversion of substituted phenols to substituted dibenzo-*p*-dioxins with a palladium-copper catalyst.



$R = H, CH_3, CH_2CH_3, OCH_3, NO_2$

Although the mechanism of the reaction has not been studied, the reaction is important in light of the widespread industrial uses of phenol and phenol derivatives.

An interesting procedure for preparation of dihydroxydibenzo-*p*-dioxins is based on the oxidative coupling of polyhalocatechols found by reduction of the resulting quinone (Frejka 1937).



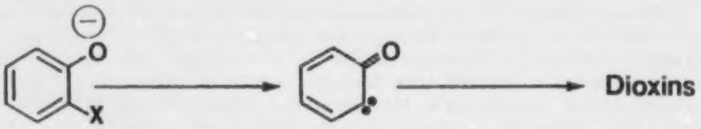
Although the yields from this process are modest (15 to 35 percent), the reaction proceeds under very mild conditions.

Discussion of Reaction Chemistry

On the basis of the data presented thus far, certain generalizations can be made about the conditions under which formation of dioxins (both halogenated and nonhalogenated) is probable.

First, and most likely, is the formation of dioxins on treatment of *o*-halophenols with base at elevated temperatures. The strength of the base required to effect this reaction depends on the particular phenol involved; however, there is adequate precedent for the ability of relatively weak organic bases such as pyridine or quinoline to effect dioxin formation. The temperature range required for dioxin formation varies with the particular *o*-halophenol; however, 1 percent yields of halogenated dioxins have been formed at temperatures as low as 145° C. (See Table 4, item 23.)

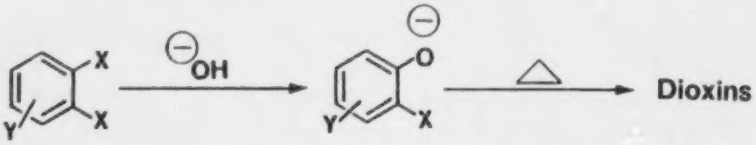
The presence of an ortho-halogen on the phenolic starting material is not an absolute requirement for dioxin formation. According to the mechanism proposed by Cadogan, Sharp, and Trattles (1974), all that is required is a substituent ortho to the phenol that is capable of acting as a leaving group.



Other substituents should be capable of elimination to give the α-ketocarbene and thus dioxins. Among those in addition to the halogens are sulfonic acids, sulfonate esters, nitro groups, and carboxylate esters.

A second possible source of dioxins is the treatment of halogenated phenols with reagents conducive to the formation of the corresponding polyhalogenated phenoxy radical (i.e., treatment with halogens or other mild oxidizing agents). Although this reaction has been used only for the preparation of perhalo dioxins (in yields of more than 80 percent and 200-gram quantities), there is no reason why the reaction could not produce the lower halogenated derivitives of dioxins. (See Table 3, item 2.)

A common practice in the preparation of polyhalobenzenes by electrophilic halogenation is neutralization of the acid byproduct with alkali hydroxides. This process (or simply a basic wash of product during the isolation procedure) can lead (via nucleophilic substitution) to a halogenated phenol, which upon distillation may produce dioxins.



The treatment of catechol salts with *o*-dihalobenzenes is a particularly efficient method for the formation of dioxins, both halogenated and nonhalogenated. Also, the treatment of polyhalocatechols with mild oxidants can produce significant quantities of halogenated dihydroxy-dioxins.

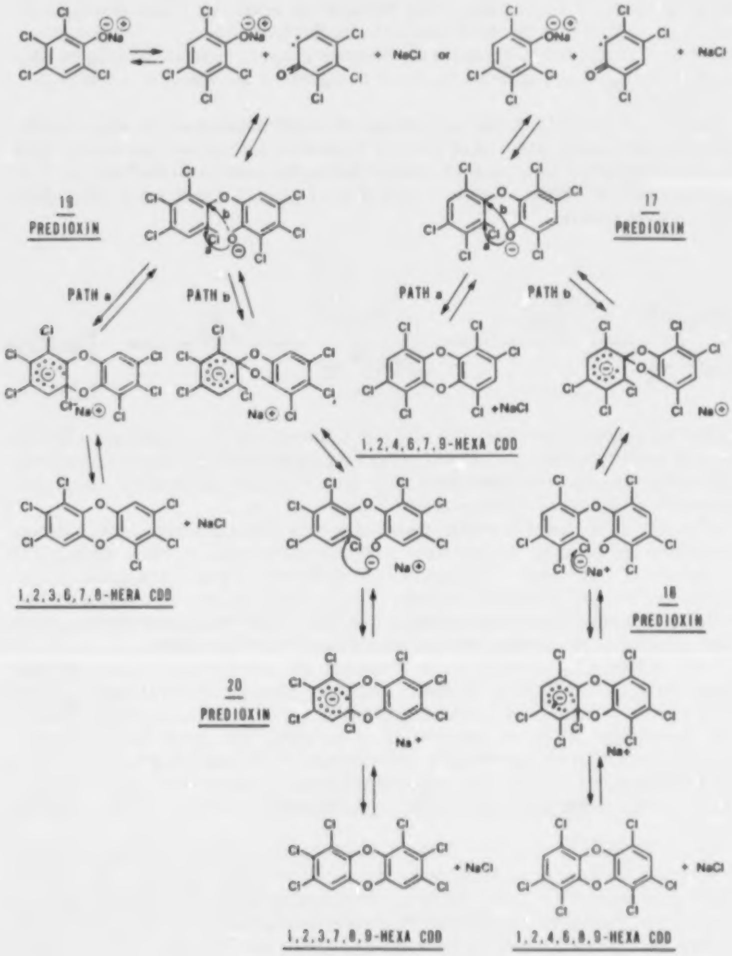
Of particular concern is the treatment of aromatic compounds under oxidizing conditions at elevated temperature. Several industrial processes involve the oxidation of benzene, toluene, and naphthalene under "semicombustion" conditions. In light of the studies such as that by Dow Chemical Company (Rawls 1979) on combustion sources of dioxins, the "tars" from these processes (which are often generated in considerable quantities) deserve further study.

The mechanistic aspects of dioxin formation discussed in this section represent the current understanding of these reactions; however, several experimental observations about dioxin formation cannot be explained by the current theories. The formation of four isomers of hexa-CDD on pyrolysis of 2,3,4,6-tetrachlorophenate (Higginbotham 1968; Langer 1973), including the 1,2,3,7,8,9-hexa-CDD (Buser 1975), can be explained in terms of the predioxin intermediates, (17) and (19), undergoing the Smiles rearrangement as shown on the following page.

As the diagram shows, the initially formed predioxin intermediate can proceed directly toward dioxin formation (path a) or can undergo the Smiles rearrangement (path b), which leads to new predioxin intermediates 18 and 20. The newly formed predioxins can then react further to give a different dioxin or can undergo the Smiles rearrangement to regenerate the original predioxin. This interconvertability of predioxins often leads to mixtures of dioxin products which are otherwise difficult to understand.

An equally disturbing mechanistic point is the observation that numerous pesticides are contaminated by polychlorodioxins, which would not be anticipated on the basis of the feedstock materials and reaction conditions. An example reported by Fishbein (1973) is the presence of significantly higher concentrations of hepta- and octachlorodioxins than hexachlorodioxin in commercial 2,3,4,6-tetrachlorophenol, also known as Dowicide-6 (see Table 9 on page 58).

The Dow Chemical Company (Rawls 1979) has proposed that the polychlorodibenzo-*p*-dioxins undergo disproportionation and establish an equilibrium mixture of halogenated dioxins. No experimental evidence in support of this proposal has been published.



SECTION 3

SOURCES OF DIOXINS

This section discusses in detail the possible sources of dioxins. The first subsection deals with the basic organic chemicals with the greatest potential for byproduct formation of dioxins. Subsequent subsections examine chlorophenols and their derivatives, hexachlorobenzene, dioxins in particulate air emissions from combustion, dioxins in plastic, and dioxins produced for research.

ORGANIC CHEMICALS

Because of the very large number of organic compounds and their varying proclivities to form dioxins, the compounds were screened initially on the basis of molecular structure, process sequence, and commercial significance.

As a means of focusing attention on those organic chemicals most likely to be associated with the formation of dioxins, they were placed in the following classifications:

> Class I—Polyhalogenated phenols, primarily with a halogen ortho to the hydroxyl group, with a high probability of dioxin formation. Products with such compounds appearing as intermediates are also considered. Manufacture of these materials normally involves reaction conditions of elevated temperature plus either alkalinity or free halogen presence, either of which is conducive to formation of halogenated dioxins.
>
> Class II—Ortho-halophenols and ortho-halophenyl ethers where the substituted groups are a mixture of halogens and nonhalogens. Processing conditions are similar to those defined for Class I and produce mixed substituted dioxins. The distinction between Classes I and II is arbitrary and does not indicate necessarily a difference in likelihood of dioxin formation.
>
> Class III—Other chemicals having the possibility, but less likelihood, of dioxin formation. These include 1) ortho substituted aromatic compounds requiring an unusual combination of reaction steps to produce dioxins, 2) aromatic compounds that might form dioxins because of their production under semicombustion conditions, and 3) products that might contain dioxins by way of contamination of their starting materials.

Since only commercially significant products are of interest in this study, the listing is limited to those produced in quantities in excess of 1000 pounds per year and/or whose sales reach $1000 per year, as required for listing in the Stanford Research Institute Directory of Chemical Producers. The product lists are based on commercial production during the past 10 years.

Table 7 lists and classifies commercial organic chemicals selected as having a relationship to dioxin formation or presence. Structures are shown for Classes I and II, the chemicals of primary importance. Class III compounds are listed by name only. In addition, Tables A1-5 in Appendix A give further information on the producers and production sites of organic chemicals.

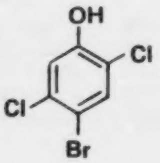
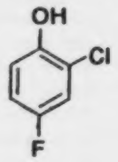
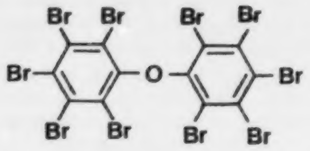
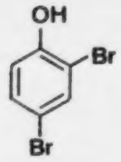
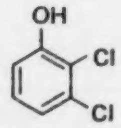
Most of the organic chemicals considered are used as manufacturing intermediates or at least are subjected to subsequent formulation or fabrication.

Thus further processing may introduce additional possibilities for dioxin formation, contamination, and exposure not contemplated within the scope of this study.

Toxicity of the many substituted dibenzo-*p*-dioxins varies widely. None are excluded from consideration here since disproportionation and other composition shifts may bring about changes from lower toxicity forms to higher (Buser 1976).

The intended reaction mechanisms for each Class I organic chemical are shown in Figures 2 through 12. The sequence is shown from left to right across the top of each figure, and the possible dioxin side reaction mechanism diverges to typical dioxin byproducts at the bottom of the figure. The specific dioxin products shown are those for which reasonably straightforward mechanisms can be postulated. In many cases more complex and secondary mechanisms may produce dioxins in addition to those shown.

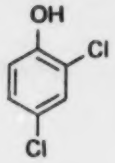
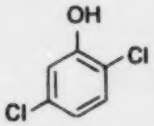
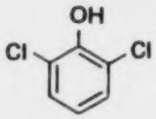
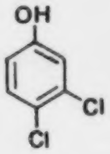
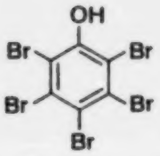
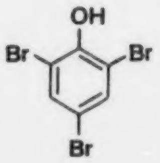
TABLE 7. ORGANIC CHEMICALS RELATED TO DIOXIN FORMATION

Class I	
4-BROMO-2,5-DICHLOROPHENOL	
2-CHLORO-4-FLUOROPHENOL	
DECABROMOPHENOXYBENZENE	
2,4-DIBROMOPHENOL	
2,3-DICHLOROPHENOL	

(continued)

TABLE 7 (continued)

Class I (continued)

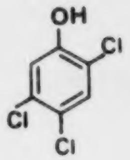
2,4-DICHLOROPHENOL	
2,5-DICHLOROPHENOL	
2,6-DICHLOROPHENOL	
3,4-DICHLOROPHENOL	
PENTABROMOPHENOL	
2,4,6-TRIBROMOPHENOL	

(continued)

TABLE 7 (continued)

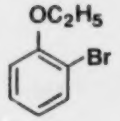
Class I (continued)

2,4,5-TRICHLOROPHENOL

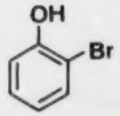


Class II

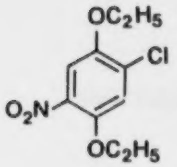
BROMOPHENETOLE



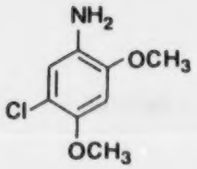
O-BROMOPHENOL



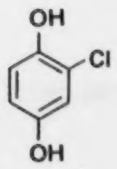
2-CHLORO-1,4-DIETHOXY-5-NITROBENZENE



5-CHLORO-2,4-DIMETHOXY-ANILINE



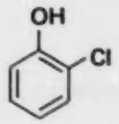
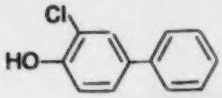
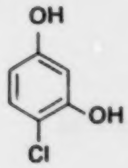
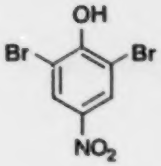
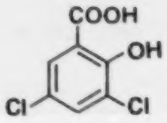
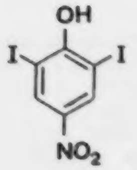
CHLOROHYDROQUINONE



(continued)

TABLE 7 (continued)

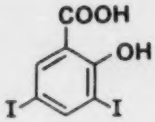
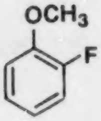
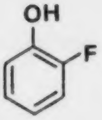
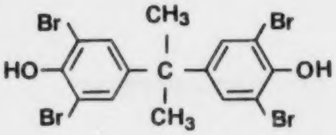
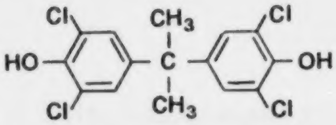
Class II (continued)

O-CHLOROPHENOL	
2-CHLORO-4-PHENYLPHENOL	
4-CHLORORESORCINOL	
2,6-DIBROMO-4-NITROPHENOL	
3,5-DICHLOROSALICYLIC ACID	
2,6-DIIODO-4-NITROPHENOL	

(continued)

TABLE 7 (continued)

Class II (continued)

3 ,5-DIIODOSALICYLIC ACID	
O-FLUOROANISOLE	
O-FLUOROPHENOL	
TETRABROMOBISPHENOL -A	
TETRACHLOROBISPHENOL-A	

Class III

3-Amino-5-chloro-2-hydroxybenzenesulfonic acid
2-Amino-4-chloro-6-nitrophenol
o-Anisidine
Benzaldehyde
Bromobenzene
o-Bromofluorobenzene

(continued)

TABLE 7 (continued)

Class III (continued)
o-Chlorofluorobenzene
3-Chloro-4-fluoro-nitrobenzene
3-Chloro-4-fluorophenol
4-Chloro-2-nitrophenol
Chloropentafluorobenzene
2,4-Dibromofluorobenzene
3,4-Dichloroaniline
o-Dichlorobenzene
3,4-Dichlorobenzaldehyde
3,4-Dichlorobenzotrichloride
3,4-Dichlorobenzotrifluoride
1,2-Dichloro-4-nitrobenzene
3,4-Dichlorophenylisocyanate
3,4-Difluoroaniline
o-Difluorobenzene
1,2-Dihydroxybenzene-3,5-disulfonic acid, disodium salt
2,5-Dihydroxybenzenesulfonic acid
2,5-Dihydroxybenzenesulfonic acid, potassium salt
2,4-Dinitrophenol
2,4-Dinitrophenoxyethanol
3,5-Dinitrosalicylic acid
Fumaric acid
Hexabromobenzene
Hexachlorobenzene
Hexafluorobenzene
Maleic acid
Maleic anhydride
o-Nitroanisole
2-Nitro-*p*-cresol
o-Nitrophenol
Pentabromochlorocyclohexane
Pentabromoethylebenzene
Pentabromotoluene
Pentachloroaniline
Pentafluoroaniline
o-Phenetidine
Phenol (from chlorobenzene)
1-Phenol-2-sulfonic acid, formaldehyde condensate
Phenyl ether
Phthalic anhydride
Picric acid
Sodium picrate
Tetrabromophthalic anhydride
1,2,4,5-Tetrachlorobenzene
Tetrachlorophthalic anhydride
Tetrafluoro-*m*-phenylenediamine
Tribromobenzene
1,2,4-Trichlorobenzene
2,4,6-Trinitroresorcinol

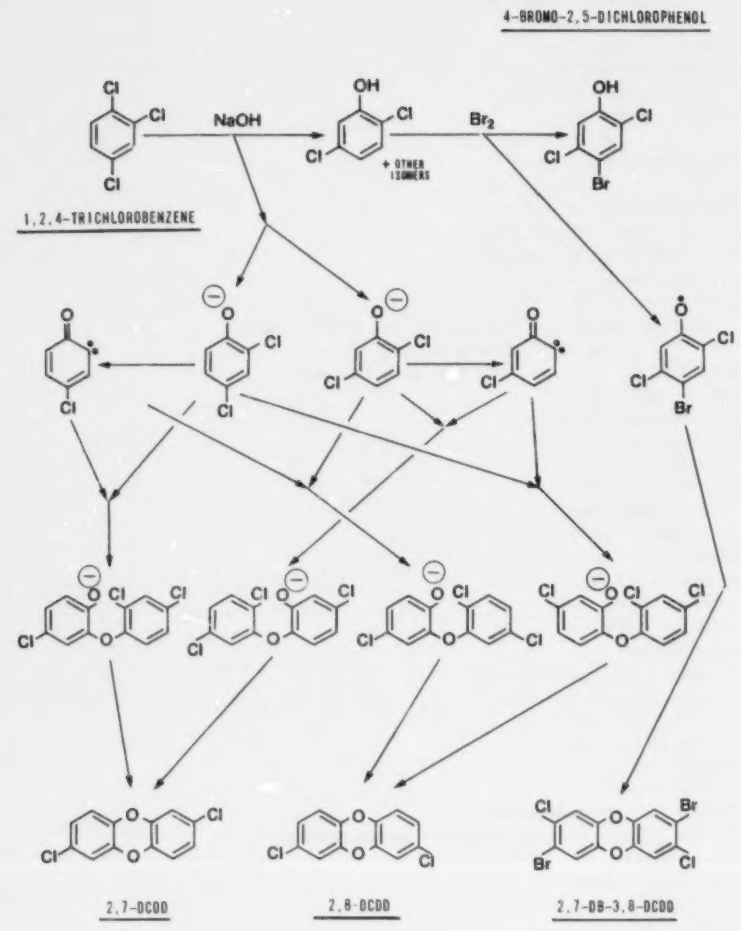


Figure 2. Proposed reaction mechanism for dioxin formation in the production of 4-bromo-2,5-dichlorophenol.

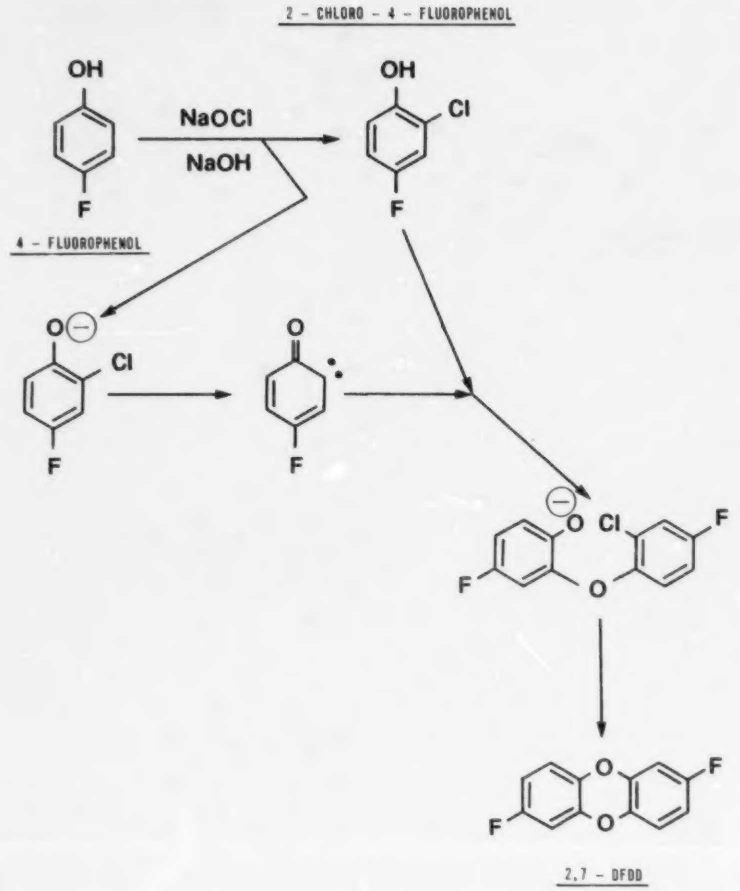


Figure 3. Proposed reaction mechanism for dioxin formation in the production of 2-chloro-4-fluorophenol.

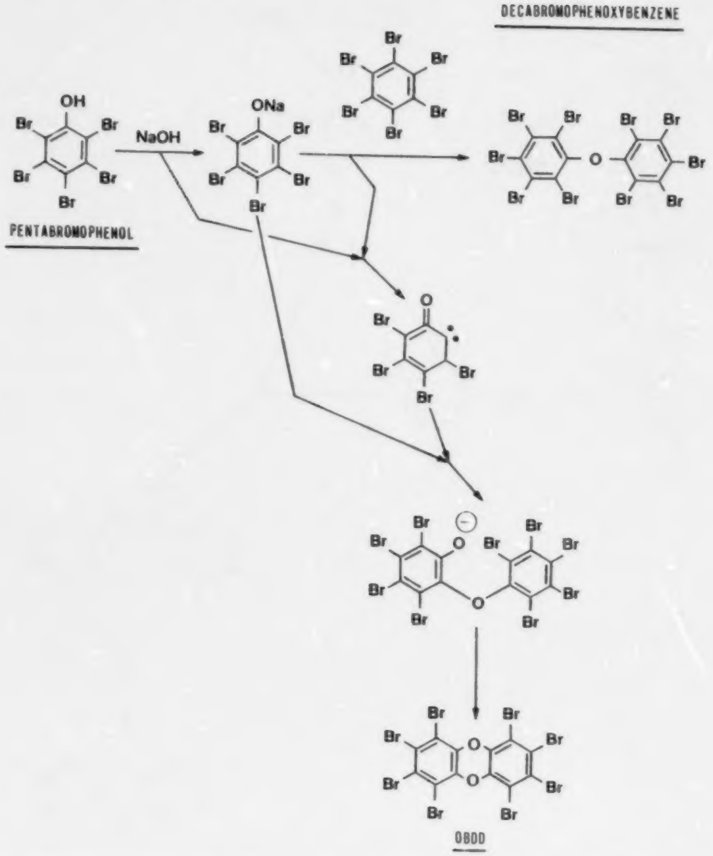


Figure 4. Proposed reaction mechanism for dioxin formation in the production of decabromophenoxybenzene.

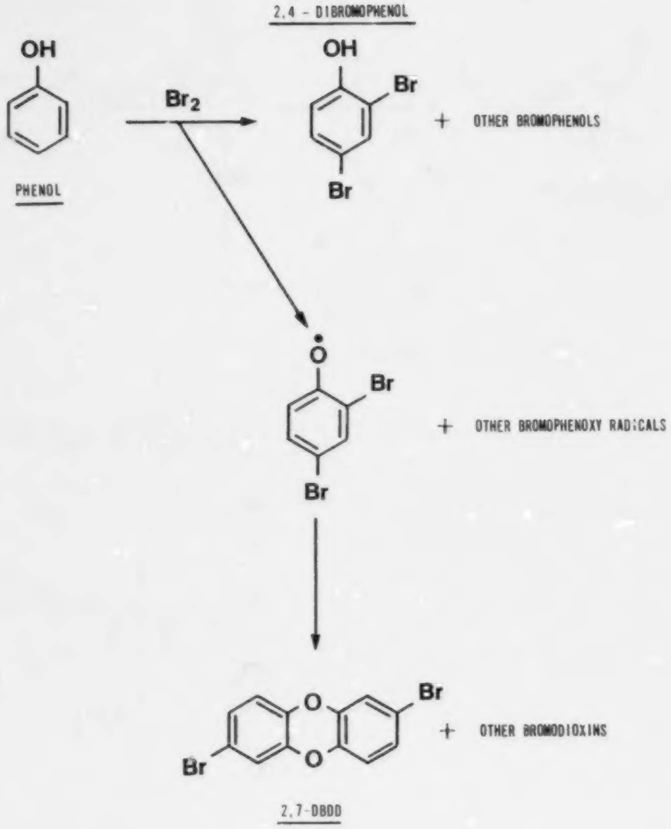


Figure 5. Proposed reaction mechanism for dioxin formation in the production of 2,4-dibromophenol.

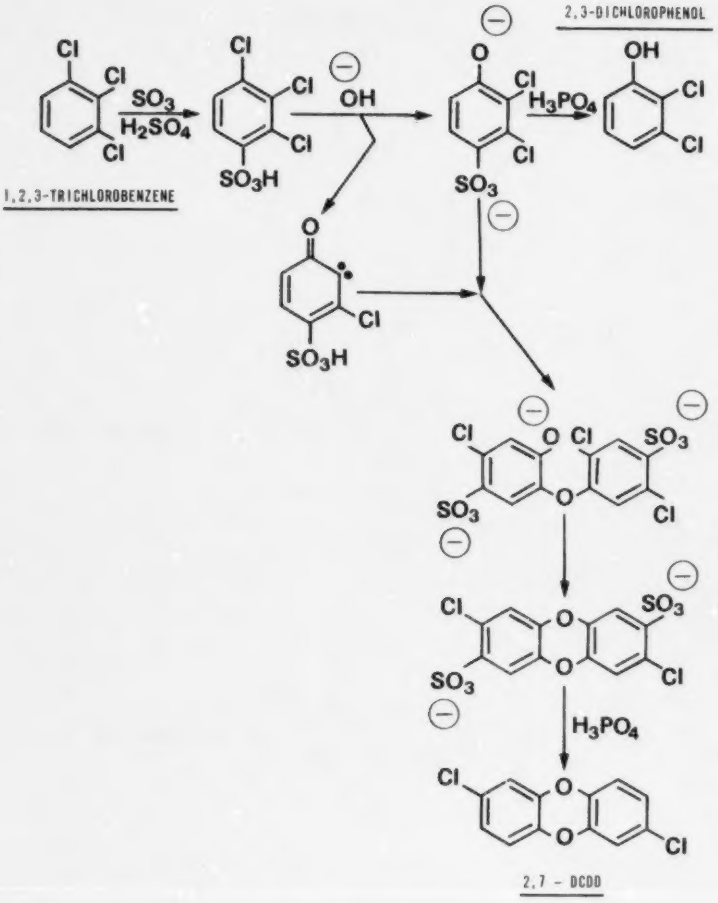


Figure 6. Proposed reaction mechanism for dioxin formation in the production of 2,3-dichlorophenol.

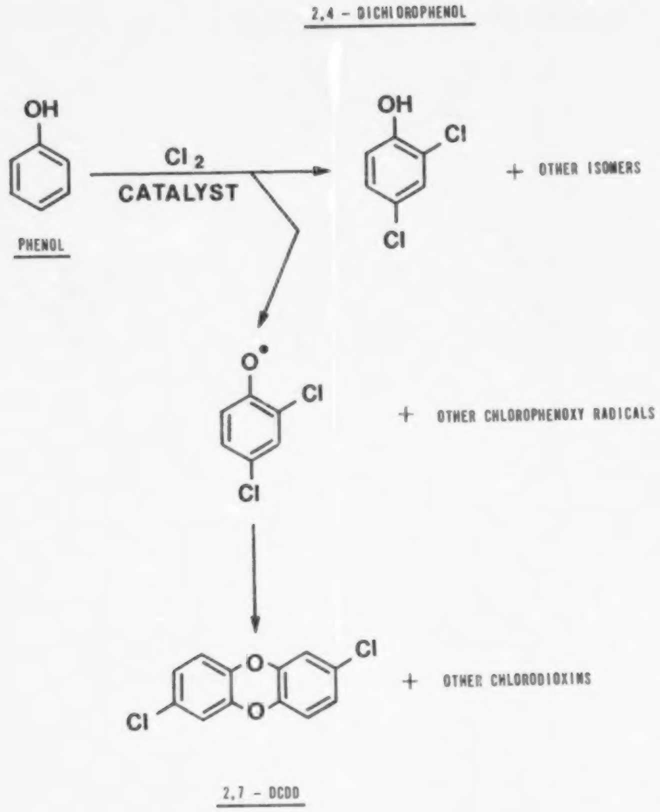


Figure 7. Proposed reaction mechanism for dioxin formation in the production of 2,4-dichlorophenol.

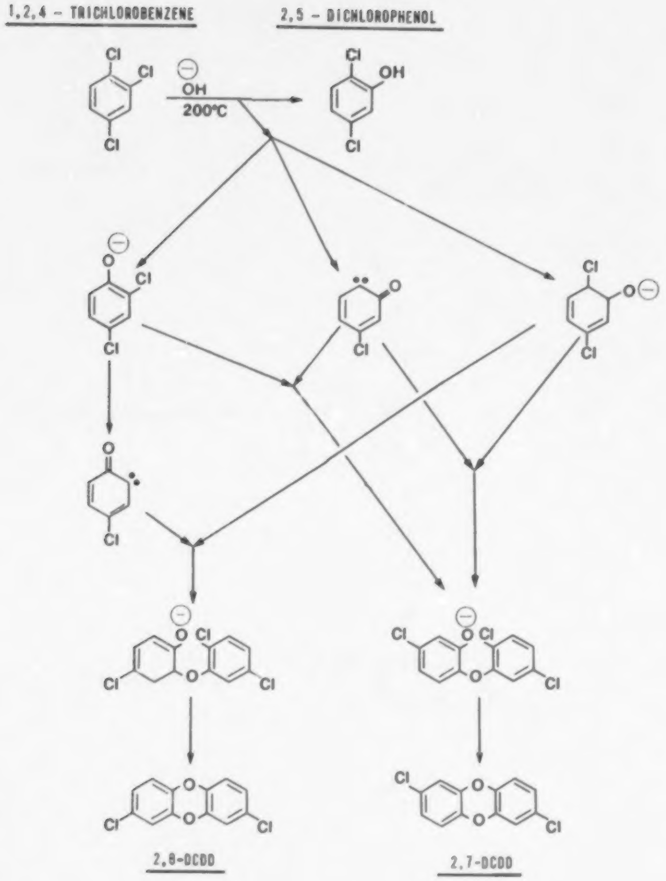


Figure 8. Proposed reaction mechanism for dioxin formation in the production of 2,5-dichlorophenol.

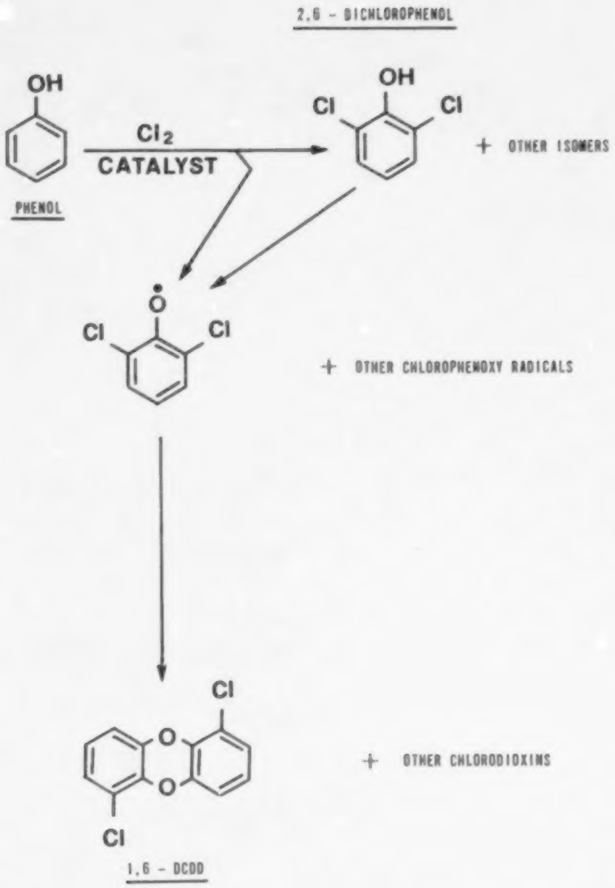


Figure 9. Proposed reaction mechanism for dioxin formation in the production of 2,6-dichlorophenol.

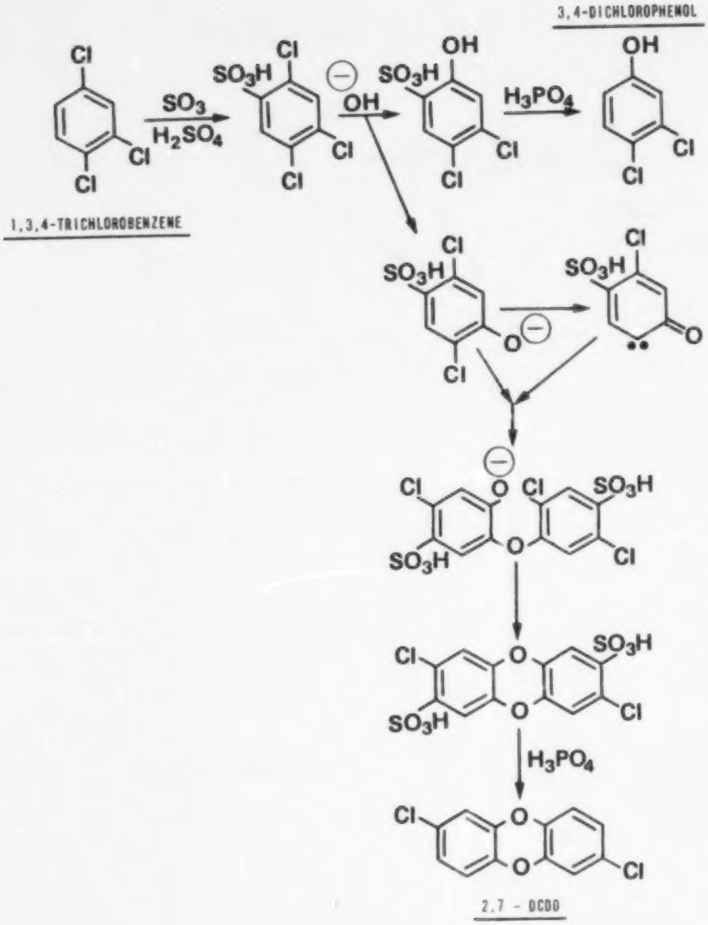


Figure 10. Proposed reaction mechanism for dioxin formation in the production of 3,4-dichlorophenol.

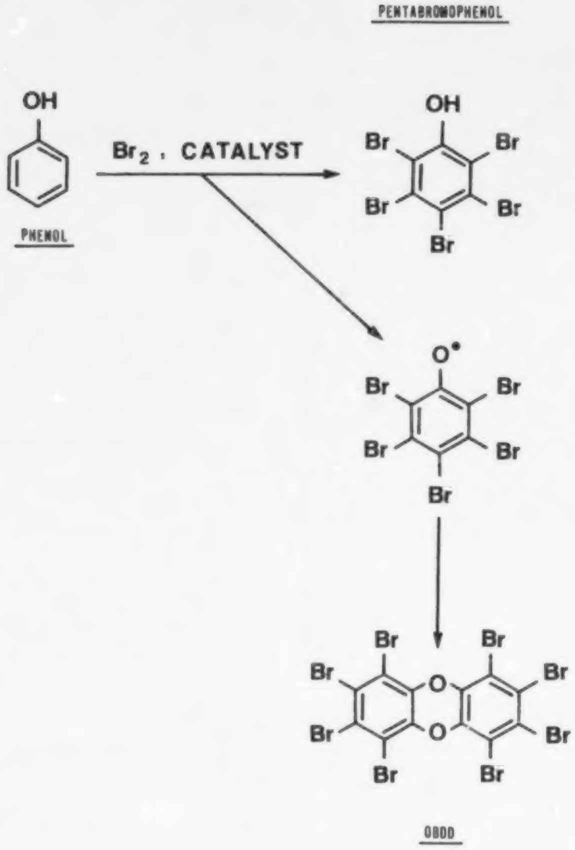


Figure 11. Proposed reaction mechanism for dioxin formation in the production of pentabromophenol.

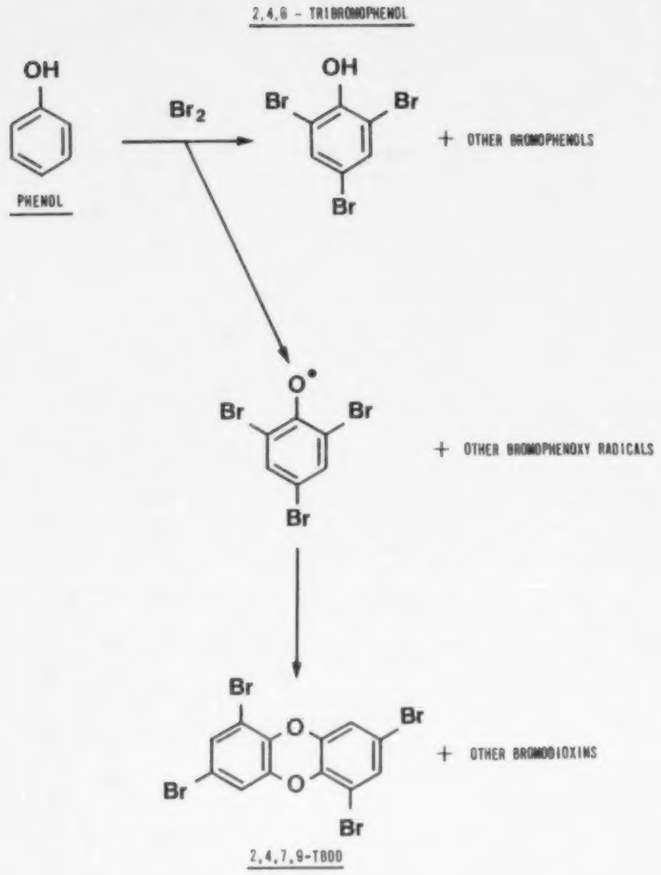


Figure 12. Proposed reaction mechanism for dioxin formation in the production of 2,4,6-tribromophenol.

PESTICIDE CHEMICALS

Pesticides are the most significant group of organic chemicals in relation to dioxin occurrence. This statement is based on the structure and reaction mechanism analogy, reaction conditions, detected presence of dioxins in a number of commercial pesticide products, and a history of environmental contamination problems, particularly with trichlorophenol and 2,4,5-T.

Chlorinated dibenzo-*p*-dioxins are known to be present in at least trace amounts in a number of pesticide chemicals. These include 2,4,5-T, silvex, 2,4-D, erbon, sesone, DMPA, ronnel, tetradifon, and the various chlorophenols (Fishbein 1973). In addition, the chemical structures, reactions, and process conditions for a number of others indicate dioxin content potential.

This study deals with production of the basic pesticide chemicals. Thus it does not address problems of dioxin formation possibly resulting from formulation, storage, distribution, and utilization of the pesticides. If exposure to alkaline formation media or elevated temperatures is encountered in any of the diverse procedures for handling and use of these pesticides, dioxin formation could be a significant problem.

Selection and Classification

The pesticide chemicals were selected for evaluation in this study on the basis of molecular structure, from those listed as commercial pesticides in the Farm Chemicals Handbook. The primary criterion was an ortho-halophenolic structure, or the derivative esters and salts thereof. Also considered were ortho dihalo aromatic structures, which conceivably could convert to phenols upon exposure to alkaline conditions.

A second criterion was a minimum commercial production level of 1000 pounds or $1000 value per year. These correspond to the minimum levels required for inclusion in the Stanford Research Institute Directory of Chemical Producers, which was a primary reference. The lists are based on production during the past 10 years.

The pesticide chemicals considered in this study are listed in Table 8. They are grouped into classes representing likelihood of dioxin formation, as follows:

Class I—Highly likely to be associated with the presence of halogenated dibenzo-*p*-dioxins because of the presence of an ortho-halogenated phenol in the reaction sequence, with subjection to elevated temperature ($\geq$145° C+) plus either alkalinity or the presence of free halogen.

Class II—Reasonable but lesser probability of such dioxin association because of the presence of phenolic or aromatic structures related to dioxins; although not directly involving dioxin precursive conditions, such chemicals might form dioxins under irregular operating conditions.

TABLE 8. LIST OF PESTICIDE CHEMICALS

General name	Chemical name
Class I	
Bifenox	Methyl-5-[2,4-dichloroephenoxy]-2-nitrobenzoate
Chloranil	2,3,5,6-Tetrachloro-2,5-cyclorhexadiene-1,4-dione

(continued)

TABLE 8. (continued)

General name	Chemical name
2,4-D and esters and salts	(2,4-Dichlorophenoxy) acetic acid and esters and salts
2,4-DB and salts	2,4-Dichlorophenoxybutyric acid and salts
Dicamba	3,6-Dichloro-2-methoxybenzoic acid
Dicamba, dimethylamine salt	3,6-Dichloro-2-methoxybenzoic acid, dimethylamine salt
Dicapthon	Phosphorothioic acid *o*-(2-chloro-4-nitrophenyl) *o,o*-dimethyl ester
Dichlofenthion	Phosphorothioic acid *o*-2,4-dichlorophenyl *o,o*-diakyl ester
Disul sodium (sesone)	2,4-Dichlorophenoxyethyl sulfate, sodium salt
2,4-DP	2-[2,4-Dichlorophenoxy] propionic acid
Erbon	2,2-Dichloropropanoic acid 2-(2,4,5-trichlorophenoxy) ethyl ester
Hexachlorophene	2,2′-Methylene bis (3,4,6-trichlorophenol)
Isobac 20	2,2′-Methylene bis (3,4,6-trichlorophenol), monosodium salt
Nitrofen	2,4-Dichlorophenyl-*p*-nitrophenyl ether
Pentachlorophenol (PCP) and salts	Pentachlorophenol and salts
Ronnel	Phosphorothioic acid, *o,o*-dimethyl 0-(2,4,5-trichlorophenyl) ester
Silvex and esters and salts	2-(2,4,5-Trichlorophenoxy) propionic acid and esters and salts
2,4,5-T and esters and salts	(2,4,5-Trichlorophenoxy) acetic acid
—	2,3,4,6-Tetrachlorophenol
—	2,4,5-Trichlorophenol
Class II	
—	*o*-Benzyl-*p*-chlorophenol
Bromoxynil and esters	3,5-Dibromo-4-hydroxybenzonitrile

(continued)

TABLE 8. (continued)

General name	Chemical name
Carbonphenothion	Phosphorodithioic acid *s*-[[(4-chlorophenyl)thio]methyl] *o,o*-diethyl ester
DCPA	2,3,5,6-Tetrachloro-1,4-benzenedicarboxylic acid dimethyl ester
Dichlone	2,3-Dichloro-1,4-haphthalenedione
Dinitrobutylphenol, ammonium salt	2,4-Dinitro-6-sec-butyl phenol, ammonium salt
Loxynil	3,5-Diiodo-4-hydroxybenzonitrile
Lindane	1,2,3,4,5,6-Hexachlorocyclohexane, gamma isomer
MCPA	(4-Chloro-*o*-toloxy) acetic acid
MCPB	4-(2-Methyl-4-chlorophenoxy) butyric acid
Mecoprop	2-(4-Chloro-2-methylphenoxy) propionic acid
Parathion	Phosphorothioic acid *o,o*-diethyl *o*-(4-nitrophenyl) ester
PCNP	Pentachloronitrobenzene
—	Pipecolinopropyl-3,4-dichlorobenzoate
Piperalin	3-(2-Methylpiperidino)propyl-3,4-dichlorobenzoate
Propanil	3,4-Dichloropropionanilide
Tetradifon	1,2,4-Trichloro-5-[(4-chlorophenyl)-sulfonyl] benzene
—	2,3,6-Trichlorobenzoic acid
—	2,3,6-Trichlorophenylacetic acid and sodium salt
—	Triiodobenzoic acid

Chemical Reactions

Higher chlorinated dioxins have been detected in samples of a number of pesticides produced from 1950 to 1970. Data from these analyses were summarized by Fishbein (1973), as shown in Table 9.

TABLE 9. HIGHER CHLORINATED DIOXINS FOUND IN COMMERCIAL PESTICIDES[a]

Pesticide	Chlorodibenzo-*p*-dioxin detected[b]				Sample	
	Tetra-	Hexa-	Hepta-	Octa-	Number contaminated	Number tested
Phenoxyalkanoates						
2,4,5-T	++	++	–	–	23	42
Silvex	+	–	–	–	1	7
2,4-D	–	+	–	–	1	24
Erbon	–	–	–	++	1	1
Sesone	–	+	–	–	1	1
Chlorophenols						
Tri-	–	+	+	+	4	6
Tetra-	–	++	++	++	3	3
Penta- (PCP)	–	++	++	++	10	11
Others[c]	–	++	++	+	5	22

a—Fishbein 1973.

b—Concentration range: ++ = >10 ppm
+ = 0.5 to 10 ppm
– = <0.5 ppm

c--DMPA, ronnel, and tetradifon were found to contain chlorodioxin contamination.

Many of the dioxins present differ from those expected on the basis of the straightforward mechanisms hypothesized. Possible reasons for this may be that other mechanisms are at work or that substantial disproportionation is occurring among the dioxins initially formed, as has been suggested by Dow Chemical Company (Rawls 1979) and others (Buser 1976).

Reaction mechanisms for the Class I pesticide products are shown in the following figures. The intended product reaction sequence is from left to right across the top of each figure, and the possible dioxin side reaction mechanism diverges to typical dioxin byproducts at the bottom of the figure. The specific dioxin products shown are those for which reasonably straightforward mechanisms can be postulated. In many cases, more complex and secondary mechanisms may produce dioxins in addition to those shown, as evidenced by their analytical detection in a number of products (Fishbein 1973).

The initial reaction steps in producing many of the Class I pesticides are very similar and thus the pesticides are grouped by common mechanism. Similarity is noted in 2,4,5-T, silvex, ronnel, 2,4-D, erbon, sesone, dichlofenthion, dicapthon, bifenox, and dicamba. The final substitution pattern differs in each case, as does the precise halophenol or chlorobenzene starting structure.

The first step in production of 2,4,5-T, silvex, ronnel, and erbon is identical (Figures 13 through 16). Treatment of 1,2,4,5-tetrachlorobenzene with caustic yields 2,4,5-trichlorophenol. The reaction conditions are sufficiently drastic, including alkalinity and elevated temperature, to cause formation of the α-ketocarbene, which reacts with the chlorophenylate to give the predioxin, which then reacts to yield 2,3,7,8-TCDD. Continued alkaline processing, which occurs with each of these product items, also contributes to the same transient intermediates and consequently to formation of 2,3,7,8-TCDD.

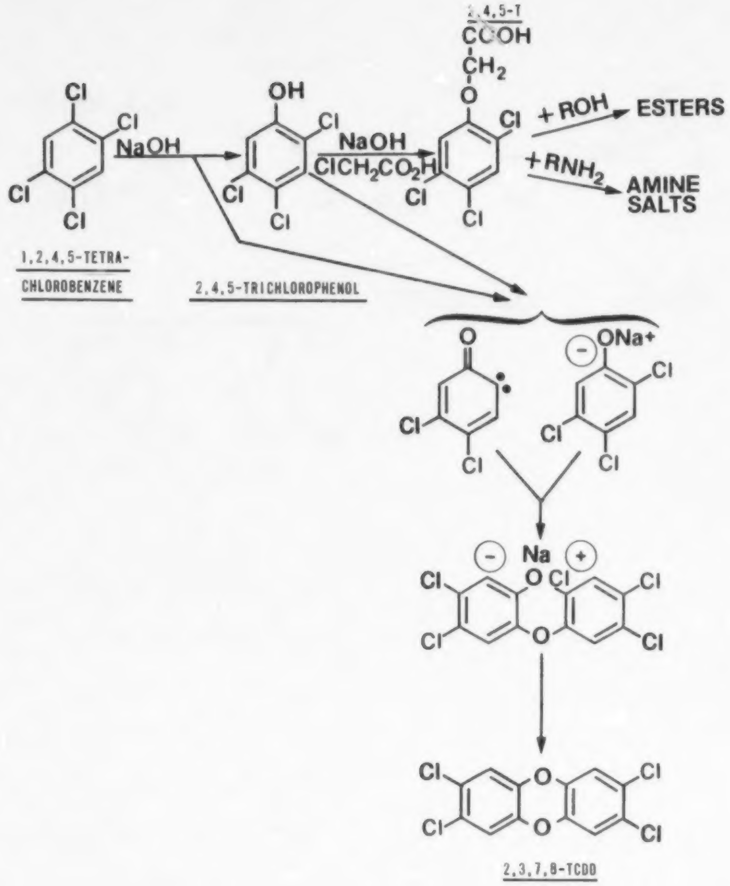


Figure 13. 2,4,5-Trichlorophenol, 2,4,5-T and esters and salts.

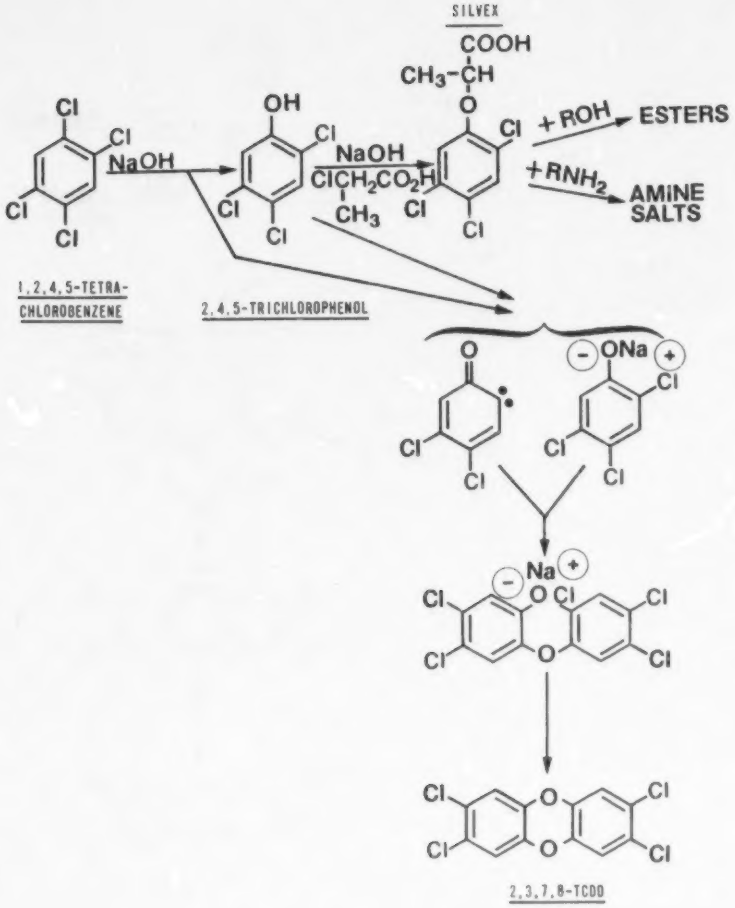


Figure 14. Silvex and esters and salts.

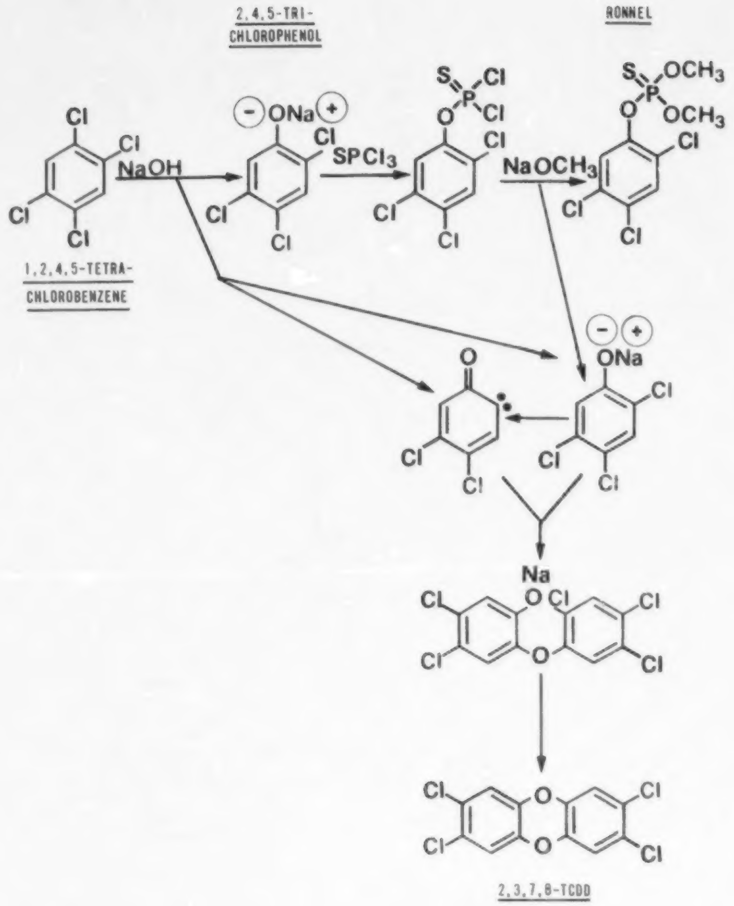


Figure 15. Ronnel.

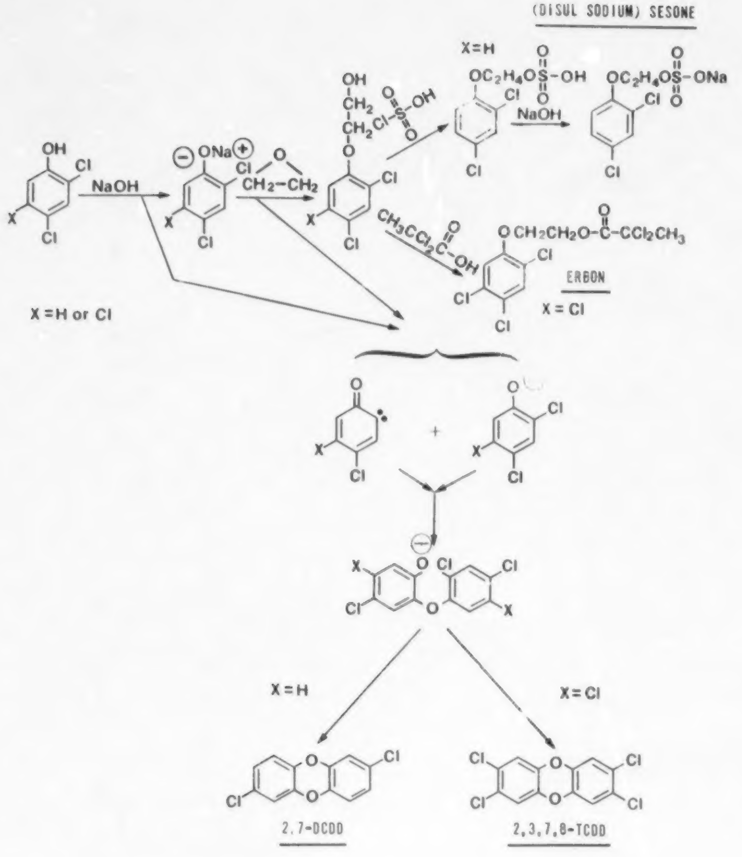


Figure 16. Erbon and sesone.

The normal reaction sequences for 2,4-D, 2,4-DB, 2,4-DP, disul sodium (sesone), dichlofenthion, bifenox, and nitrofen (sequences shown in Figures 16 through 22) are analogous in their early steps to those of 2,4,5-T and others in the group just described, but occur via 2,4-dichlorophenol rather than 2,4,5-trichlorophenol. The dioxin formation sequence is likewise analogous but typically would produce 2,7-DCDD.

Note that the reaction mechanism for disul sodium is presented in the same figure (Figure 16) with that for erbon. This placement is not meant to imply that they are co-products, but rather is intended to demonstrate the analogous reaction patterns of typical pesticides differing as to halogenation and substitutions. Similar analogies can be drawn among nearly all of the pesticide chemicals studied.

Another point, important to dioxin formation, is demonstrated in Figure 17, showing the reaction for 2,4-D. The reaction sequence conventionally cited is chlorination of phenol to 2,4-dichlorophenol, followed by a reaction with chloroacetic acid in the presence of caustic to produce 2,4-D. This last step with the dichlorophenol under alkaline conditions can result in dioxin formation. An alternative process sequence cited in the patent literature (Manske 1949) reverses the order of chlorination, as shown in the upper tier reaction of Figure 16. This sequence would be expected to reduce the likelihood of dioxin formation. A commercially feasible yield in excess of 80 percent is noted, but the extent of commercial utilization is not known. This reaction sequence could possibly be adapted to other dihalogenated phenoxyalkanoates, with an expected reduction in dioxin formation.

Dicamba (Figure 23) with its dimethylamine salt presents one of the more complex dioxin derivation patterns because of the continued alkaline conditions under which various substitutions are made. First, preparation of 2,5-dichlorophenol and its subsequent further exposure to caustic results in transient intermediates and predioxins that form 2,7-DCDD and 2,8-DCDD. In addition, similar alkaline processing of the carboxyl and methyl substituted forms can result in variously substituted dioxins, only two of which, for simplicity, are shown in Figure 23.

Pentachlorophenol (PCP), a commercially high-volume chemical, can be manufactured by two basic methods. One involves direct chlorination of phenol (Figure 24) in the presence of an $AlCl_3$ catalyst. The presence of normal excess chlorine is conducive to formation of a free-radical intermediate, then of the predioxin, and ultimately of OCDD. The alternative process based on caustic treatment of hexachlorobenzene (Figure 25) produces chlorinated transient intermediates analogous to the 2,4,5-T series but fully chlorine substituted. These in turn form the predioxin and finally OCDD.

The complex free-radical mechanism by which chloranil is made (Figure 26) results in transient intermediates similar to those occurring as byproduct derivatives of PCP. Therefore, OCDD should be expected as a dioxin contaminant.

Hexachlorophene and its sodium salt, Isobac 20 (Figure 27), are produced from 2,4,5-trichlorophenol whose preliminary production from 1,2,4,5-tetrachlorobenzene is carried out by reaction with caustic. This first step potentially forms dioxin precursors similar to the equivalent step in the manufacture of 2,4,5-T. Consequently, 2,3,7,8-TCDD is the anticipated byproduct dioxin.

The production of 2,3,4,6-tetrachlorophenol (Figure 28) by chlorination of phenol would be expected to yield trace byproducts of various isomeric hexachlorodibenzo-*p*-dioxins via a free-radical mechanism.

Again, because of the analytical evidence of many dioxins other than those hypothesized in these mechanisms, no specific dioxin presence should be presumed or excluded.

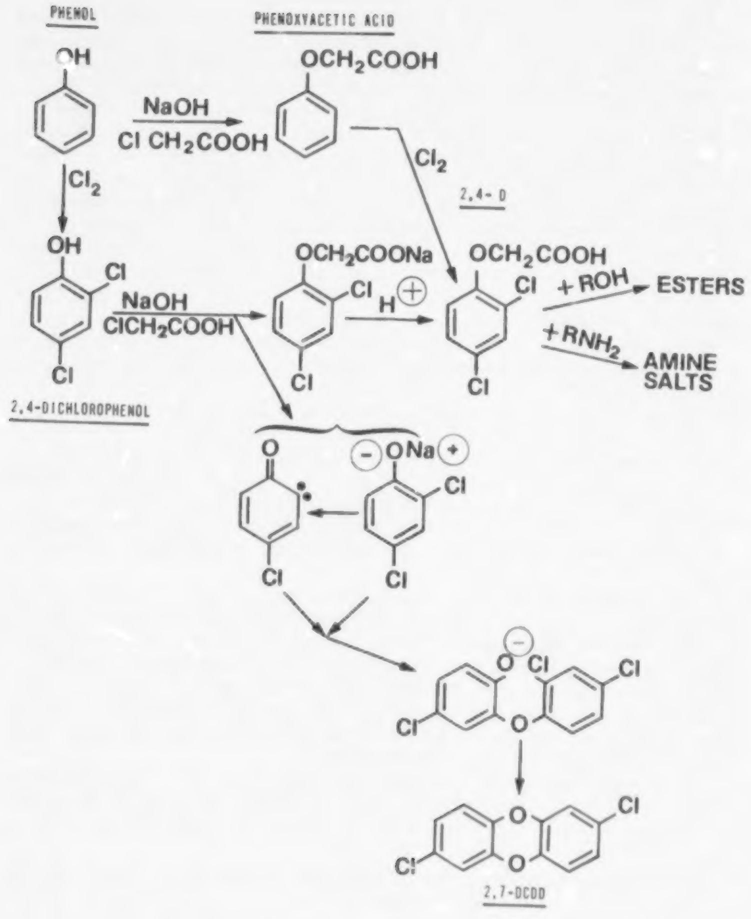


Figure 17. 2,4-D and esters and salts.

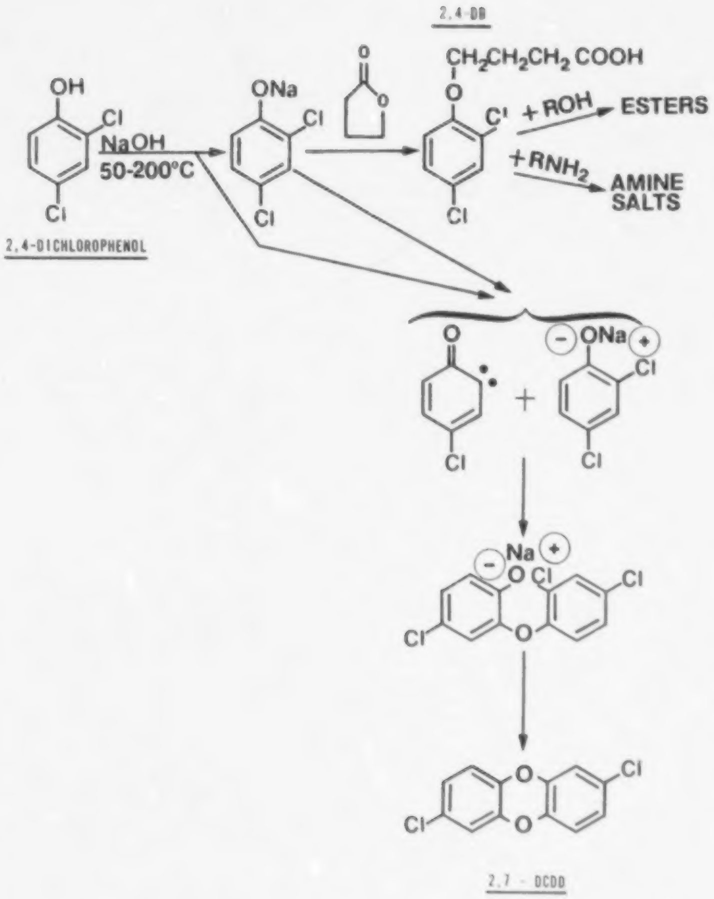


Figure 18. 2,4-DB.

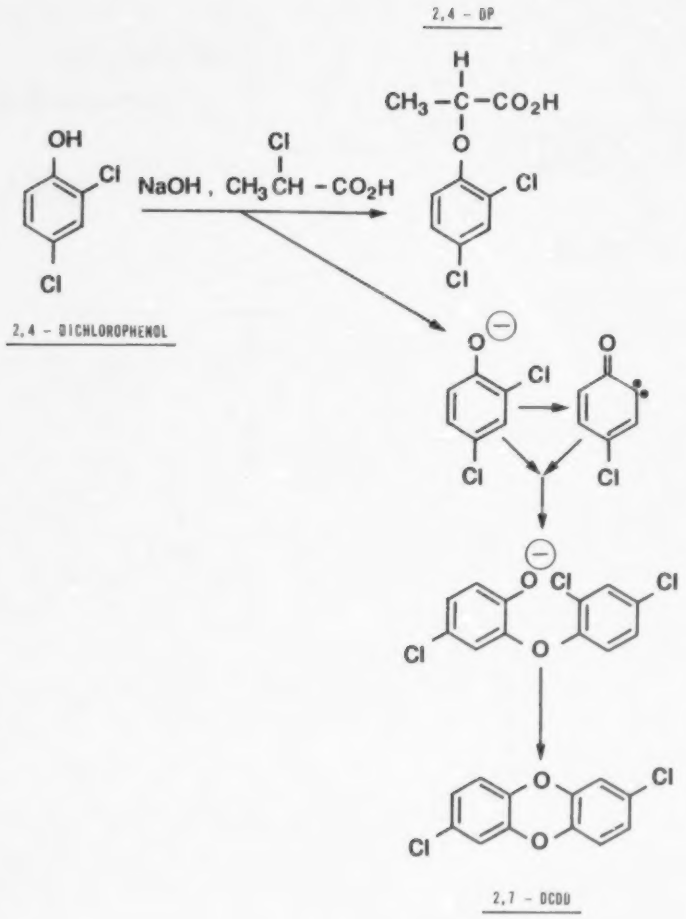


Figure 19. 2,4-DP

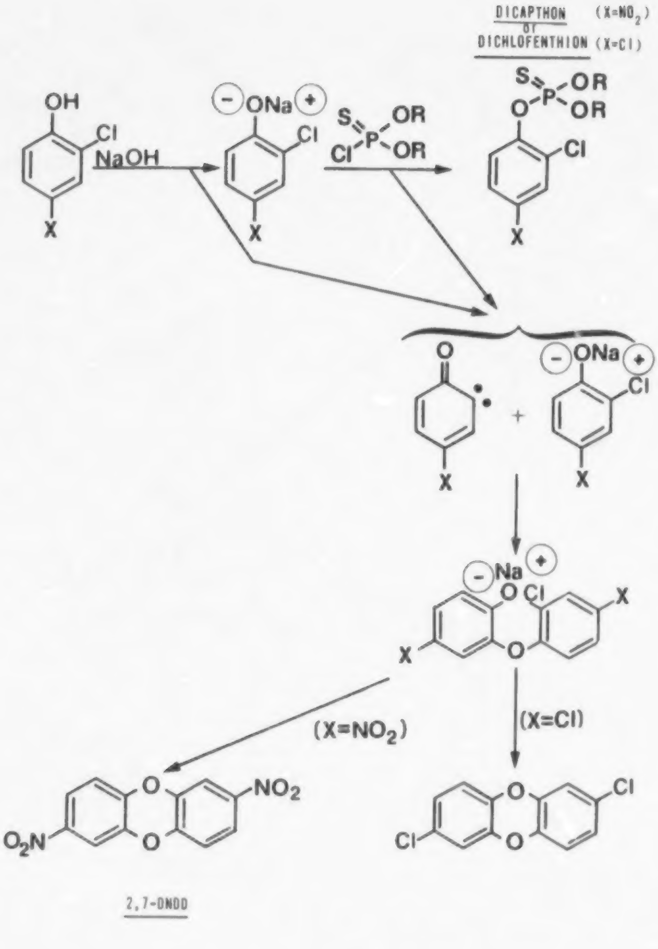


Figure 20. Dicapthon and dichlofenthion.

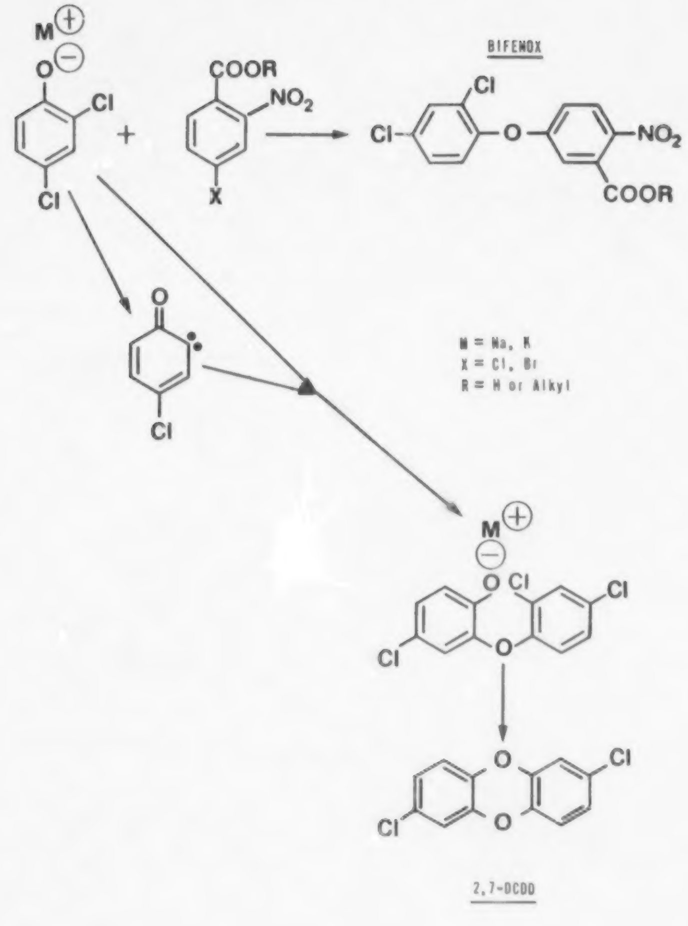


Figure 21. Bifenox.

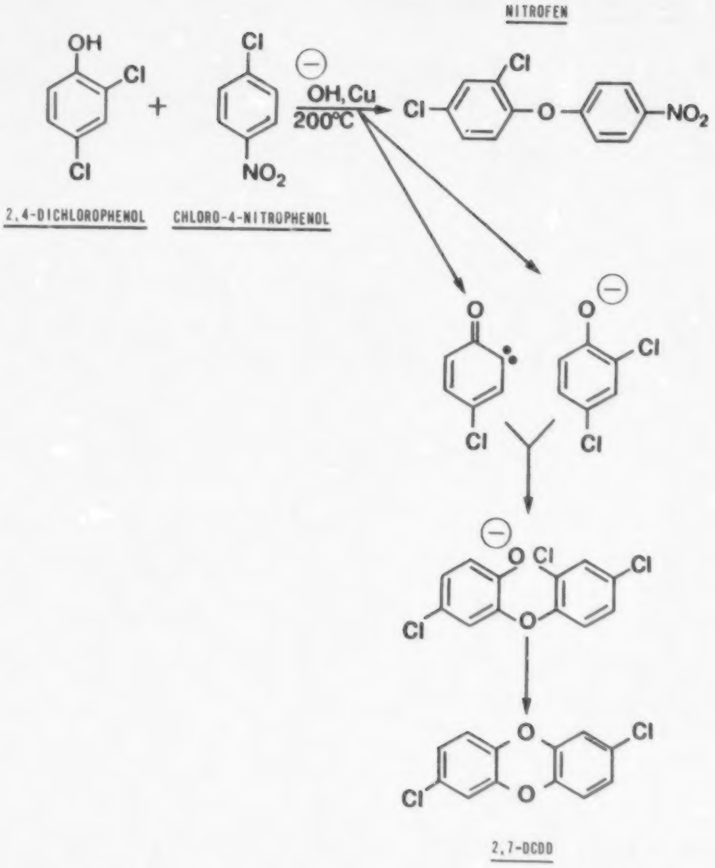


Figure 22. Nitrofen.

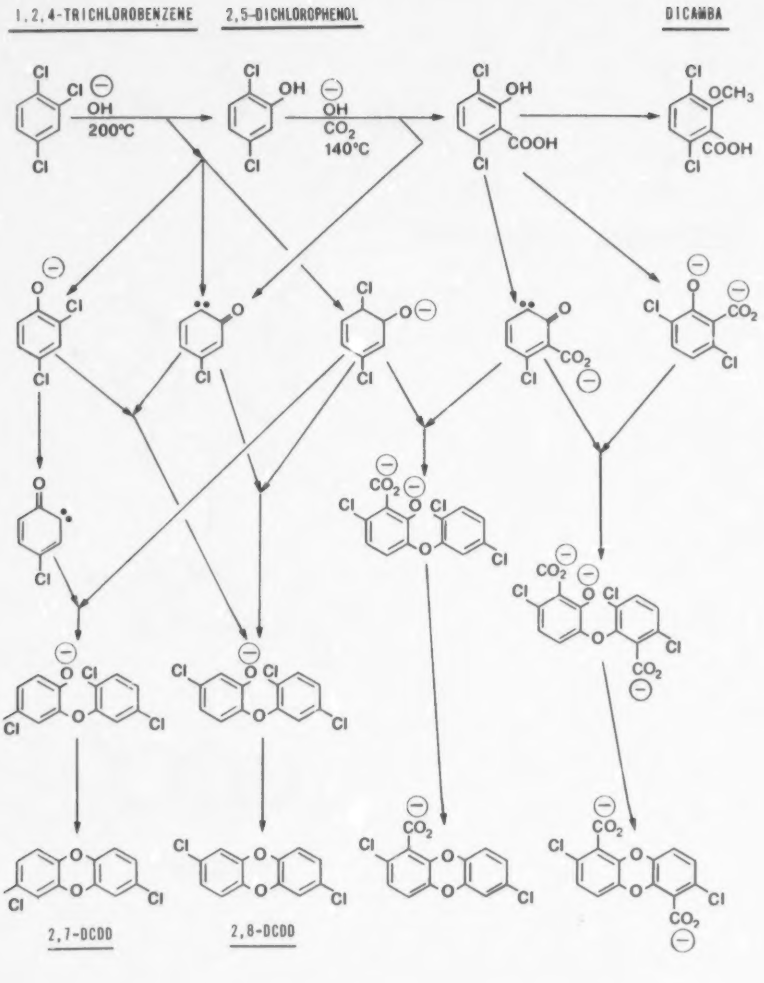


Figure 23. Dicamba.

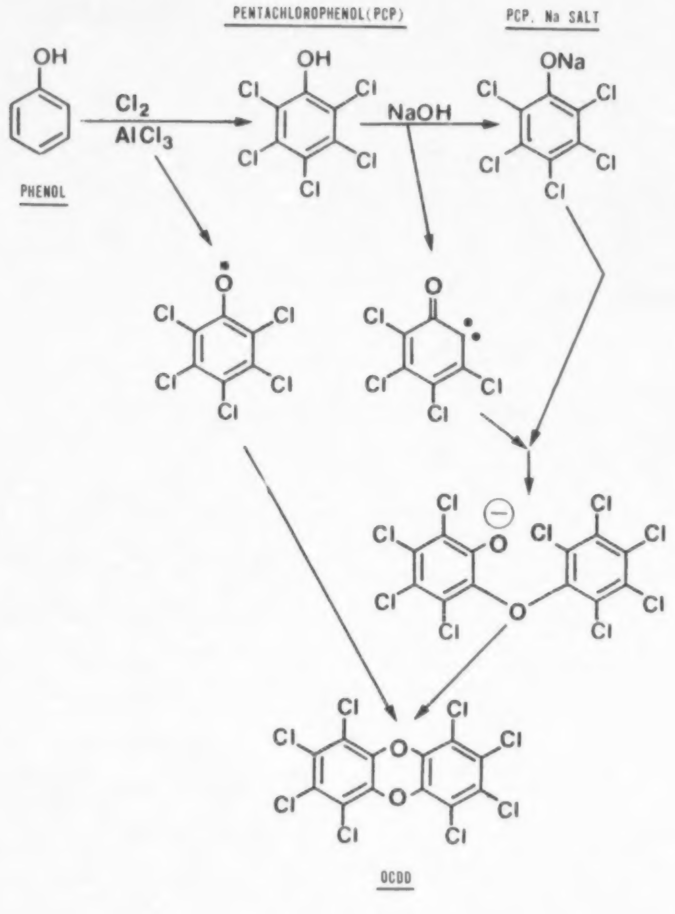


Figure 24. Pentachlorophenol (PCP) via phenol.

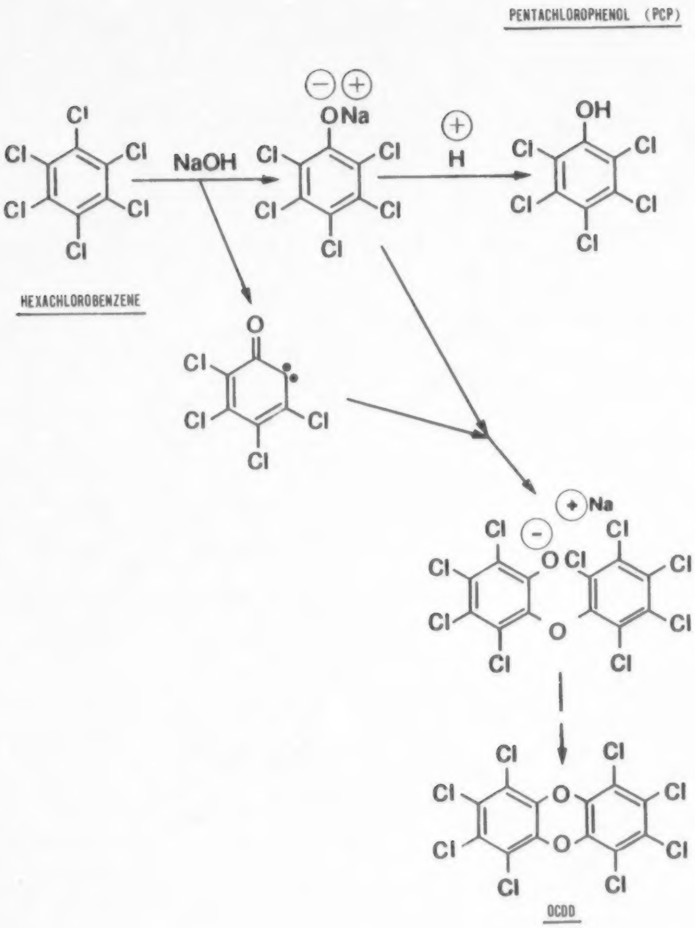


Figure 25. Pentachlorophenol (PCP) via hexachlorobenzene.

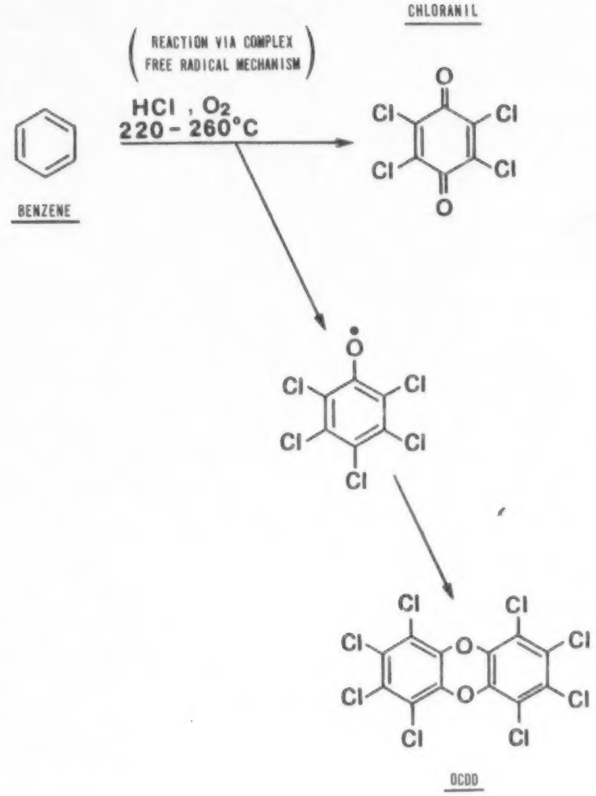


Figure 26. Chloranil.

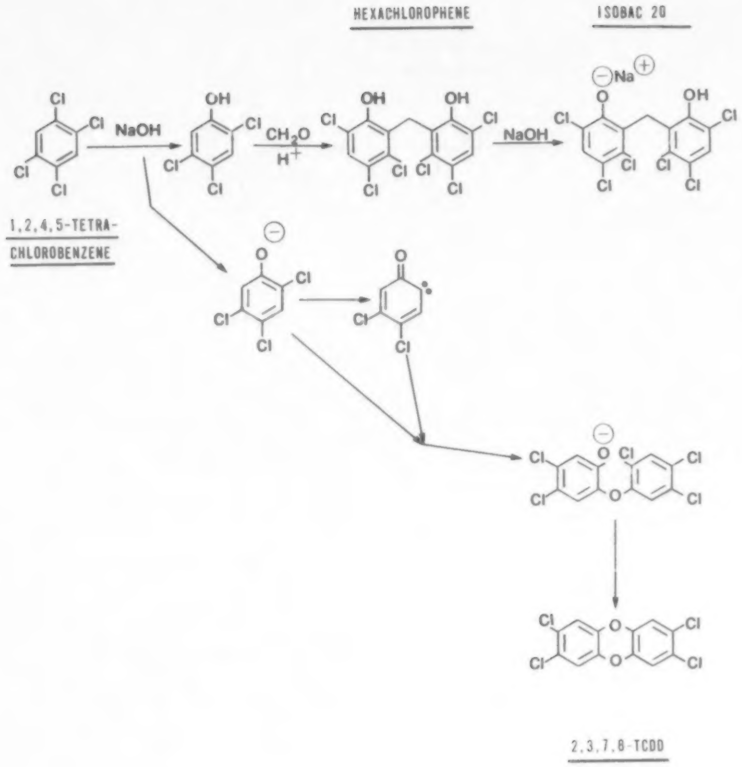


Figure 27. Hexachlorophene and Isobac 20.

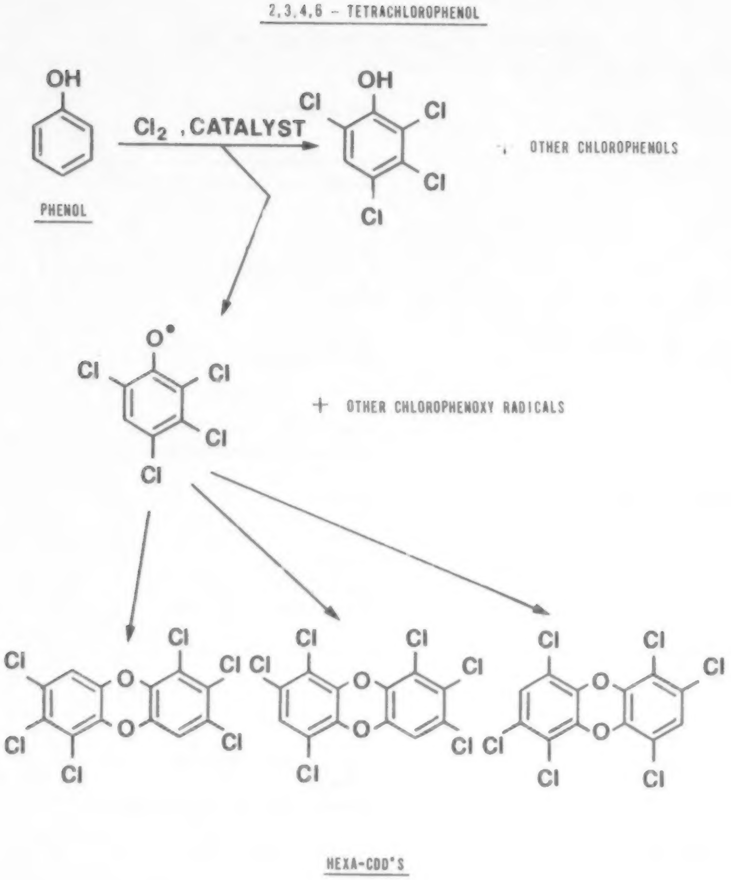


Figure 28. 2,3,4,6-Tetrachlorophenol.

Table 10 summarizes the primary raw materials involved in the production of the Class I pesticide chemicals.

A more complete discussion of many of these pesticides appears in the following subsections.

TABLE 10. PESTICIDE RAW MATERIALS

Pesticide product	Raw materials
Bifenox	2,4-Dichlorophenol 3-Halo-*o*-nitrobenzoic acid ester NaOH
Chloranil	Benzene Hydrogen chloride Oxygen
2,4-D and esters and salts	Phenol Chloroacetic acid NaOH Cl_2 Alcohols (for esters) Amines (for amine salts)
2,4-DB and salts	Phenol Cl_2 NaOH Butyrolactone Alcohols (for esters) Amines (for amine salts)
Dicamba	1,2,4-Trichlorobenzene NaOH CO_2 Dimethyl sulfate
Dicapthon	2-Chloro-4-nitrophenol NaOH Chlorodimethylthiophosphonate
Dichlofention	2,4-Dichlorophenol NaOH Chlorodimethylthiophosphonate
Disul sodium (sesone)	2,4-Dichlorophenol NaOH Ethylene oxide Chlorosulfonic acid
2,4-DP	2,4-Dichlorophenol 2-Chloropropionic acid NaOH

(continued)

TABLE 10. (continued)

Pesticide product	Raw materials
Erbon	1,2,4,5-Tetrachlorobenzene NaOH Ethylene oxide 2,2-Dichloropropionic acid
Hexachlorophene and Isobac 20	1,2,4,5-Tetrachlorobenzene NaOH Ethylene oxide
Nitrofen	2,4-Dichlorophenol Chloro-4-nitrobenzene KOH
Pentachlorophenol (PCP)	Phenol Cl_2 (Phenol route) or Benzene Cl_2 (Hexachlorobenzene route) NaOH
Ronnel	1,2,4,5-Tetrachlorobenzene NaOH Phosphorus sulfochloride $NaOCH_3$
Silvex and esters and salts	1,2,4,5-Tetrachlorobenzene NaOH Chloropropionic acid Alcohols (for esters) Amines (for amine salts)
2,4,5-T and esters and salts	1,2,4,5-Tetrachlorobenzene NaOH Chloracetic acid Alcohols (for esters) Amines (for amine salts)
2,3,4,6-Tetrachlorophenol	Phenol Cl_2
2,4,5-Trichlorophenol	1,2,4,5-Tetrachlorobenzene NaOH

DIOXINS IN COMMERCIAL CHLOROPHENOLS AND THEIR DERIVATIVES

Since most reports of dioxins are associated with chlorinated phenolic compounds, this section examines this group of organic materials with respect to their reported dioxin contaminants and their utilization, manufacture, production volumes, and derivatives. Similar information is presented, when available, for hexachlorobenzene, which has been found to contain dioxins, and also for a group of other related commercial chemicals that theoretically could contain dioxin contaminants, although no analyses have been reported. For each chemical, the discussions include the probable processing steps that may promote dioxin formation and also the mechanisms through which dioxins could appear in the associated process wastes or be retained within the chemical products.

Chlorophenols

Chlorinated phenols are a family of 19 compounds, consisting of a benzene ring to which is attached one hydroxyl group and from one to five chlorine atoms. The positions of the chlorine atoms with respect to the hydroxyl group and to each other provide the opportunity for three monochlorophenols, six each of dichloro- and trichlorophenols, three tetrachlorophenols, and one pentachlorophenol. Many researchers have established the presence of dioxins in these chemicals; Table 11 lists the results of several such studies.

Data in this table show that until recently dioxins have not been found in commercially produced mono- or dichlorophenols. The presence of 2,3,7,8-TCDD in low concentration was found in 1979 in a railroad tank car spill of *o*-chlorophenol. One or more samples of all chlorophenols with three or more chlorine atoms that have been examined have contained dioxins. TCDD's have been identified not only in the 2,4,5-trichloro isomer but also in the 2,4,6-trichloro isomer. One or more samples of trichlorophenol have contained dioxins with two to eight chlorine substituents. Only dioxins with six to eight chlorine substituents have been found in tetra- and pentachlorophenol. Numerous analyses have confirmed that dioxins with less than six chlorine substituents are not found in pentachlorophenol.

Most commercial chlorophenols are used as raw materials in the synthesis of other organic compounds. Some of the less highly chlorinated phenols are used with formaldehyde to make fire-resistant thermosetting plastics (Doedens 1964). Those containing three or more chlorine atoms are used directly as pesticide chemicals. 2,4,6-Trichlorophenol is effective as a fungicide, herbicide, and defoliant (Hawley 1971). It was formerly used in large quantities in the leather-tanning industry; however, its use in this industry has decreased substantially (U.S. Environmental Protection Agency 1978a), probably as a result of the improved effectiveness and mass production of 2,4,5-trichlorophenol, a substance of sufficient importance to warrant a special section in this report. 2,3,4,6-Tetrachlorophenol is used as a preservative for wood, latex, and leather, and also as an insecticide (Kozak et al. 1979).

Pentachlorophenol or its sodium salt is said to be the second most widely used pesticide in the United States. It is effective in the control of certain bacteria, yeasts, slime molds, algae, fungi, plants, insects, and snails. Because of its broad spectrum, pentachlorophenol is used in many ways:

- As a preservative for wood, wood products, leather, burlap, cordage, starches, dextrins, and glues
- As an insecticide on masonry for termite control

TABLE 11. CHLORODIOXINS REPORTED IN CHLOROPHENOLS

Chlorophenol sample	Chlorodioxins (-CDD's), ppm[a]								Data source
	mono-CDD's	DCDD's	tri-CDD's	TCDD's	penta-CDD's	hexa-CDD's	hepta-CDD's	OCDD	
Monochlorophenol									
2-chlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone 1972
o-chlorophenol	-	-	-	0.037 (2,3,7,8)[b]	-	-	-	-	Chemical Week 1979
Dichlorophenol									
2,4-dichlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone 1972
2,6-dichlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone 1972
Trichlorophenol									
2,4,5-trichlorophenol (1969)	ND	ND	ND	0.30 (1,3,6,8) 6.20 (2,3,7,8)	ND	ND	ND	ND	Firestone 1972
2,4,5-trichlorophenol (1970)	ND	ND	ND	ND	1.5	ND	ND	ND	Firestone 1972
2,4,5-trichlorophenol (1970)	ND	ND	ND	ND	ND	ND	ND	ND	Firestone 1972
2,4,5-trichlorophenol (1970)	ND	ND	ND	0.07 (2,3,7,8)	ND	ND	ND	ND	Firestone 1972
Na-2,4,5-trichlorophenol (1967)	ND	ND	ND	ND	ND	ND	ND	ND	Firestone 1972
Na-2,4,5-trichlorophenol (1969)	ND	0.72 (2,7)	ND	1.40 (2,3,7,8)	ND	ND	ND	ND	Firestone 1972
2,4,5-trichlorophenol	-	-	-	0.30 (2,3,7,8)	-	-	-	-	Elvidge 1971
2,4,6-trichlorophenol	ND	ND	93 (2,3,7)	49 (1,3,6,8)	ND	ND	ND	ND	Firestone 1972
trichlorophenol	-	-	-	ND (0.5)	-	0.5-10	0.5-10	0.5-10	Woolson et al. 1972

(continued)

TABLE 11. (continued)

	Chlorodioxins (-CDD's), ppm[a]								
Chlorophenol sample	**mono-CDD's**	**DCDD's**	**tri-CDD's**	**TCDD's**	**penta-CDD's**	**hexa-CDD's**	**hepta-CDD's**	**OCDD**	**Data source**
Tetrachlorophenol									
2,3,4,6-tetrachlorophenol (Dowicide 6)	-	-	-	-	-	6	-	-	Buser 1975
2,3,4,6-tetrachlorophenol	ND	ND	ND	ND	ND	29	5.1	0.17	Firestone 1972
2,3,4,6-tetrachlorophenol (1967)	ND	ND	ND	ND	ND	4.1	ND	ND	Firestone 1972
2,3,4,6-tetrachlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone 1972
tetrachlorophenol	-	-	-	ND (0.5)	-	10-100	10-100	10-100	Woolson et al. 1972
Pentachlorophenol									
PCP (Dowicide 7)	-	-	-	-	-	9	235	250	Buser 1975
PCP	-	-	-	ND (0.5)	-	10-100	100-1000	100-1000	Woolson 1972
Na-PCP (1967)	ND	ND	ND	ND	ND	14	14.5	3.8	Firestone 1972
Na-PCP (1969)	ND	ND	ND	ND	ND	22	11.3	3.3	Firestone 1972
PCP (1970)	ND	ND	ND	ND	ND	39	49	15	Firestone 1972
PCP (1970)	ND	ND	ND	ND	ND	35	23	ND	Firestone 1972
PCP (1967)	ND	ND	ND	ND	ND	0.17	ND	ND	Firestone 1972
PCP (1969)	ND	ND	ND	ND	ND	13	47	ND	Firestone 1972
PCP (1970)	ND	ND	ND	ND	ND	0.91	2.1	5.3	Firestone 1972
PCP (1970)	ND	ND	ND	ND	ND	15	23	15	Firestone 1972
PCP (1978)	-	-	-	ND (0.1)	-	19	140	432	Dioxin in Industrial Sludges 1978
Pentachlorophenate	-	-	-	-	-	-	+	+	Jensen and Renberg 1972
PCP formulation	-	-	-	-	-	-	870	50-3300	Jensen and Renberg 1972
PCP (technical grade)	-	-	-	ND	-	33-42	19-24	7-11	Villanueva 1973
PCP (reagent grade)	-	-	-	ND	-	0.02-0.03	0.04-0.06	0.02-0.03	Villanueva 1973

(continued)

TABLE 11. (continued)

Chlorophenol sample	Chlorodioxins (-CDD's), ppm[a] mono-CDD's	DCDD's	tri-CDD's	TCDD's	penta-CDD's	hexa-CDD's	hepta-CDD's	OCDD	Data source
PCP (many samples)	–	–	–	ND	–	9–27	90–135	575–2510	PCP—A wood preservative 1977
PCP's (17)	–	–	–	–	–	0–23	–	0–3600	Crummett 1975
PCP or PCP-Na (7)	–	–	–	–	–	0.03–10	0.6–180	5.5–370	Buser and Bosshardt 1976
PCP (Dowicide 7 1970)	–	–	–	–	–	4	125	2500	PCP Ad Hoc Study Report 12/78 SAB
PCP (Dowicide 7 1970) (distilled)	–	–	–	–	–	1.0	6.5	15	PCP Ad Hoc Study Report 12/78 SAB
PCP	–	–	–	–	–	9–27	–	575–2510	Johnson et al. 1973
Na-PCP (Dowicide G 1978)	–	–	–	–	–	ND–2	1–12	4–173	Dow Chemical Company 1978

a—Key to abbreviations and symbols: ND = Not detected (minimum detection level, ppm). Other numbers in parentheses indicate year chlorophenol sample was obtained, or specific dioxin detected.
– = Not analyzed or not reported.

b—Presence of 2,3,7,8-TCDD confirmed but not quantitatively reported.

- As a fungicide/slimicide in pulp and paper mills, in cooling tower waters, and in evaporation condensors
- As a preharvest weed defoliant on seed crops
- As a preservative on beans (for replanting only)
- As a means of controlling slimes in secondary oil recovery injection water (in the petroleum industry)

By far the major use of pentachlorophenol is as a wood preservative. It was once reported to have been used in shampoos; however, this chemical does not now appear to be used as an ingredient in cosmetics or drugs, since it is not listed either in the CTFA Cosmetic Ingredient Dictionary (Cosmetic, Toiletry, and Fragrance Association, Inc. 1977), or in the Physicians' Desk Reference (1978).

Manufacture—

Through either process variations or separation of mixtures by fractional distillation, manufacturers selectively produce chlorophenols with specific numbers and arrangements of chlorine atoms. Table 12 shows that 13 of the 19 possible chlorophenols are currently sold commercially in sufficient volume to be listed in the 1978 Stanford Research Institute Directory of Chemical Producers. Seven of these are made in much higher volume than the other six. The high-volume products are all made by one of two major types of manufacturing processes, referred to herein as the hydrolysis method and the direct chlorination method.

As mentioned earlier, chlorophenols are benzene rings that contain one hydroxyl group and one or more chlorine atoms. The basic raw material in the manufacture of chlorophenols is benzene, and the two major manufacturing methods differ primarily in the order in which the substituents are attached to the benzene ring. In the hydrolysis method, chlorophenols are made by replacing one chlorine substituent of a polychlorinated benzene with a hydroxyl group. The hydrolysis method is the only practical method for producing some of the chlorophenols, such as the 2,4,5 isomer; this isomer is apparently the only one currently produced in large quantity by this method (Kozak 1979; Deinzer 1979; Chemical Engineering 1978). In the direct chlorination method, phenol (hydroxybenzene) is reacted with chlorine to form a variety of chlorophenols. Each manufacturing method is more fully described in the paragraphs below. In addition, a detailed description of the manufacture of 2,4,5-trichlorophenol (2,4,5-TCP) is outlined separately.

Hydrolysis method—The first step in the hydrolysis method is the direct chlorination of benzene. Through a series of distillations, rechlorinations, and other chemical treatments, several purified chlorobenzene compounds are obtained that contain from two to six chlorine substituents. Specific chlorophenols are then made by reacting one of the chlorine substituents with caustic, thereby replacing the chlorine atom with a hydroxyl group (see Figure 29). The reaction takes place in a solvent in which both materials are soluble, and the mixture is held at specific conditions of temperature and pressure until the reaction is complete. The product is then recovered from the reaction mixture. The solvent is usually an alcohol (most often methanol), although use of other solvents is possible.

A 1957 process patent describes the manufacture of pentachlorophenol from a starting material of hexachlorobenzene (U.S. Patent Office 1957e). Methanol is the solvent, and the reaction takes place at temperatures of 125° to 175° C and pressures of 125 to 360 psi. Reaction time is 0.3 to 3 hours. This method is known to have been used commercially (Arsenault 1976).

A variation of this process using ethylene glycol as the solvent also has been used commercially for the production of 2,4,5-trichlorophenol (Commoner and Scott 1976a; Whiteside 1977).

A process described in another 1957 patent uses water as the solvent in hydrolysis of dichloro- and trichlorobenzenes (U.S. Patent Office 1957c). Temperature is maintained from 240° C to 300° C under alkaline conditions at autogenous pressure. Reaction time varies from 0.5 to 3 hours. By this method, monochlorophenols are produced in yields greater than 70 percent from *o*-, *m*-, and *p*-dichlorobenzene. Metachlorophenol is formed as an impurity from the ortho- and para- starting materials through ring rearrangement mechanisms. Orthochlorophenol, which is the most likely dioxin precursor, is not formed by ring rearrangement but is produced in 86 percent yield from *o*-dichlorobenzene. Also, hydrolysis of 1,2,4-trichlorobenzene forms a mixture of dichlorophenol isomers in yields up to 95 percent.

TABLE 12. COMMERCIAL CHLOROPHENOLS AND THEIR PRODUCERS[a]

Chlorophenol	Manufacturer(s)
o-Chlorophenol	Dow Chemical Company Monsanto Company
m-Chlorophenol	Eastman Kodak Company Aldrich Chemical Company Specialty Organics, Inc. R.S.A. Corporation
p-Chlorophenol	Dow Chemical Company Monsanto Company
2,3-Dichlorophenol	Specialty Organics, Inc.
2,4-Dichlorophenol	Dow Chemical Company Monsanto Company Rhodia, Inc. Vertac, Inc.
2,5-Dichlorophenol	Velsicol Chemical Corporation
2,6-Dichlorophenol	Aldrich Chemical Company Specialty Organics, Inc.
3,4-Dichlorophenol	Aldrich Chemical Company
3,5-Dichlorophenol	Aldrich Chemical Company Specialty Organics, Inc.
2,4,5-Trichlorophenol	Dow Chemical Company Vertac, Inc.
2,4,6-Trichlorophenol	Dow Chemical Company
2,3,4,6-Tetrachlorophenol	Dow Chemical Company
Pentachlorophenol	Dow Chemical Company Vulcan Materials Company Reichold Chemicals

a—Source: Stanford Research Institute Directory of Chemical Producers, U.S. 1978.

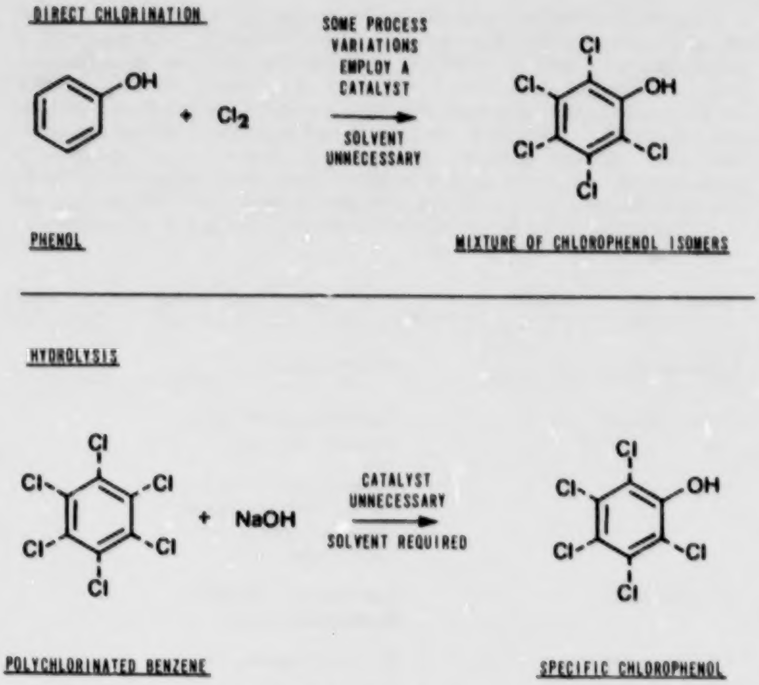


Figure 29. Basic chlorophenol reactions.

A 1967 patent describes the use of a combined methanol-water solvent system (U.S. Patent Office 1967b). Temperature is maintained at 170° to 200° C, under above-autogenous pressures. Reaction time is 1 hour or less.

A 1969 patent describes still another solvent, dimethylsulfoxide (DMSO) (U.S. Patent Office 1969). Use of this solvent in a mixture with water permits the reaction to take place at atmospheric pressure; caustic hydrolysis of hexachlorobenzene to pentachlorophenol occurs at approximately 155° C and is complete in about 3 hours. This process apparently has never been applied commercially.

When an alcohol is used as a solvent, the chemical mechanism that occurs involves an initial equilibrium reaction between the alcohol and caustic to form a sodium alkoxide, which is the reagent that actually attacks the chlorobenzene. The compound formed first is the alcohol ether of the chlorophenol. On standing, rearrangement of the compound occurs to form the chlorophenate plus any of several side reaction products (Sidwell 1976). This mechanism is significant because it explains the "aging" step that is a distinct phase in commercial hydrolysis sequences, and it also explains the substantial quantity of byproduct impurities that are derived from the alcohol solvents.

In all these processes, the product is recovered through either of two methods. In one, extraction into benzene separates the organic materials from water, salt, and excess caustic. Subsequent vacuum distillation reclaims the benzene for recycle and also separates the chlorophenols into purified fractions. Extraction with benzene (or a similar solvent) is probably the preferred product recovery method for chlorophenols of lower molecular weight, especially the mono- and dichloroproducts, since they are more easily distilled than the heavier products.

The alternative product recovery method is to filter the reaction mixture, perhaps after partial neutralization or evaporation and subsequent cooling, to reclaim unreacted polychlorobenzenes. The solution is then acidified and filtered again to collect the solid products. This variation is probably best suited to recovery of tri-, tetra-, and pentachlorophenols because these products and their raw materials are solids at room temperature and therefore can be removed more easily in the filtration operations.

Chlorophenols can be purified by distillation to separate high-boiling impurities. Technical feasibility has been reported in three 1974 patents, in which purified pentachlorophenol is recovered in good yield by high vacuum distillation in the presence of chemical stabilizers (U.S. Patent Office 1974a, 1974b, 1974c). Purification of 2,4,5-trichlorophenol by distillation has also been reported (World Health Organization 1977).

The high-temperature, high-pressure, and strongly alkaline conditions of the hydrolysis process are conducive to the formation of dioxin compounds. Although not in present U.S. commercial use, the hydrolysis manufacture of pentachlorophenol was especially favorable for the formation of octachlorodibenzo-*p*-dioxin (OCDD)(Figure 25, p. 72). As described in more detail later in this section, the commercial hydrolysis method is known to produce 2,3,7,8-TCDD from 1,2,4,5-tetrachlorobenzene.

Direct chlorination method—Direct chlorination begins by the addition of a hydroxyl group to benzene to form hydroxybenzene or phenol. This compound is manufactured in specialized plants, usually through sulfonation, chlorination, or catalytic oxidation of benzene. Dioxins have not been reported as resulting from this portion of the process; this study is therefore concerned only with the second part of the process in which phenol is reacted with chlorine to form various chlorophenols.

The reaction of phenol with chlorine actually forms a mixture of chlorinated phenols (see Figure 29), although certain compounds are formed preferentially. Direct chlorination is practical, therefore, only if the desired product is one of the high-yield compounds. Except for low-volume specialty isomers and the high-volume 2,4,5 isomer, all commercial chlorophenols made in this country are those that are formed preferentially by this process (Buser 1978; Kozak 1979; Deinzer 1979; Chemical Engineering 1978). These include mono- and dichlorophenols that are substituted at positions 2 and 4, the symmetrical 2,4,6-trichlorophenol isomer, 2,3,4,6-tetrachlorophenol, and pentachlorophenol.

Chlorination of phenol can be accomplished in batch reactors, but is best suited to the continuous process shown in simplified form in Figure 30 (U.S. Patent Office 1960; Sittig 1969). Liquid phenol and/or lower chlorinated phenols are passed countercurrently with chlorine gas through a series of reaction vessels. Trace amounts of aluminum chloride catalyst are added, usually as a separate feed into an intermediate vessel. Equipment is sized so that all the chlorine is absorbed by the phenol; the last phenol-containing vessel is usually built as a scrubbing column to ensure complete chlorine absorption. Gas leaving the scrubber is anhydrous hydrogen chloride, which is either used in other chemical operations or dissolved in water to form substantially pure hydrochloric acid as a byproduct.

The chlorophenol compound created in greatest amount by this process is established by the ratio of feed rates of chlorine and phenol. Because all chlorine is consumed, it is fed at rates 1 to 5 times the molecular proportion of phenol, depending on the principal product desired. To prevent excessive oxidation that produces nonphenolic chlorinated organic compounds, temperatures are carefully regulated; the usual temperatures are 130° to 190° C for pentachlorophenol and 170° C for 2,4-dichlorophenol. Pressure is atmospheric, and reaction time is 5 to 15 hours (U.S. Patent Office 1960).

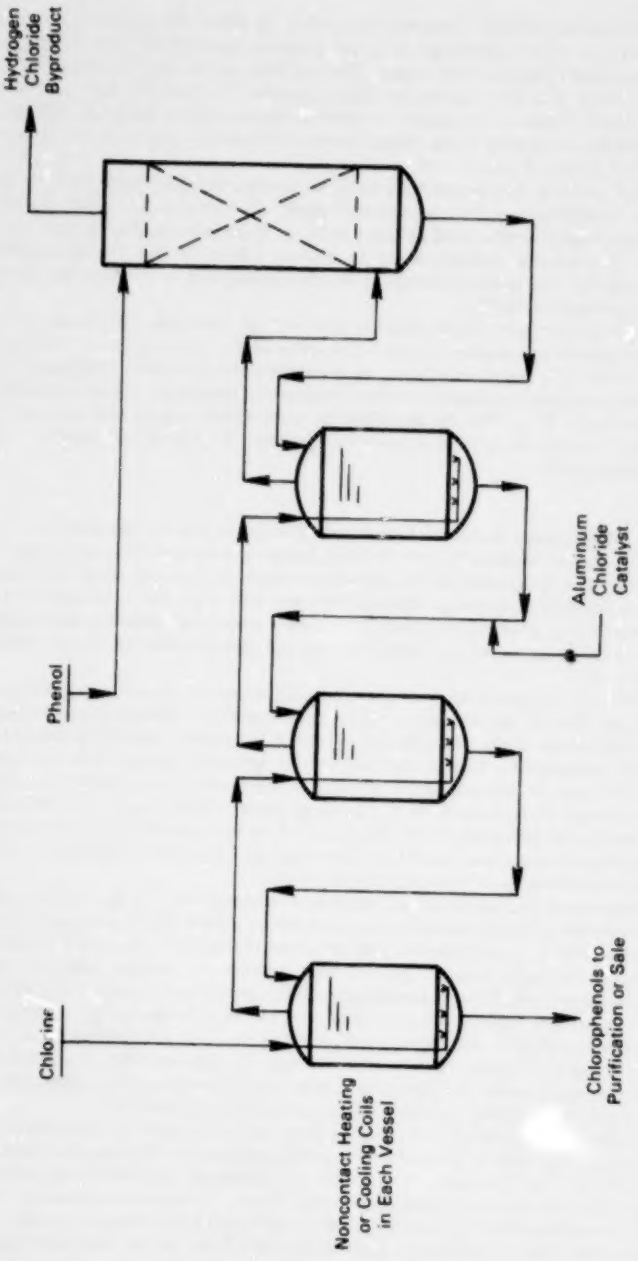


Figure 30. Direct chlorination of phenol.

The mixture from the first reaction vessel can be vacuum-distilled to separate the various compounds. Unreacted phenol and any undesired less-chlorinated phenols would be recycled. To make some products for which purity standards are rather flexible, very little purification is necessary, and some processes may include no final distillation or other treatment. Also, a chlorinated product may be withdrawn from the scrubber (usually a mixture of 2- and 4-mono- or 2,4-dichlorophenol) and may be either distilled, with portions recycled to the first reactor for further chlorination, or sold as is. 2,4-Dichlorophenol may be further processed to the phenoxy herbicide 2,4-D.

Supplemental processing steps may be necessary to remove contaminants such as "hexachlorophenol" (hexachlorocyclohexadiene-1,4-one-3), dioxins, and furans from PCP made by this process. Hexachlorophenol may be formed during the process by overchlorination of the reaction mass (U.S. Patent Office 1939). Dioxins may be formed during distillation by the condensation of PCP with itself or with hexachlorophenol (see Table 3; see also Figure 24, p. 71).

Dioxins have been reported in numerous samples of PCP, as shown in Table 8. Although hexa-CDD's, hepta-CDD's, and OCDD are known to be present in commercial PCP, 2,3,7,8-TCDD has never been found (Chemical Regulation Reporter 1978; U.S. Environmental Protection Agency 1978e).

All PCP made in the United States is produced by the direct chlorination of phenol; apparently the method involving the hydrolysis of hexachlorobenzene has never been used commercially for PCP production (American Wood Preservers Institute 1977). Dow reportedly changed its production process in 1972 to produce a PCP with lower dioxin content; the other two producers of PCP apparently have not followed Dow's lead (Chemical Regulation Reporter 1978). Details of Dow's process change were not reported.

Production—

Production figures for di- and tetrachlorophenols are not available. Although current figures for pentachlorophenol production are also not available, it is estimated from production capacity information (Table 13) that U.S. manufacturers are producing as much as 53 million pounds of PCP annually. Annual U.S. trichlorophenol production is probably also in the range of 50 million pounds (Crosby, Moilanen, and Wong 1973).

As Table 12 indicates, chlorophenols are apparently manufactured by at least 11 companies, which represent two diverse groups of chemical producers. Of the 13 commercial chlorophenols, 7 are made by Dow Chemical Company in Midland, Michigan. Except for 2,4,5-trichlorophenol, all of the isomers made by Dow are those formed preferentially through direct chlorination of phenol. Competitive with Dow in the sale of these seven chlorophenols are four other companies:

Monsanto Company—Sauget, Illinois
Reichold Chemicals, Inc.—Tacoma, Washington
Vulcan Materials Company—Wichita, Kansas
Rhodia, Inc.—Freeport, Texas

All of these companies are engaged for the most part in the mass production of organic chemicals for which market demand is relatively constant. These companies are geared to heavy chemical production, and their products are made to commercial standards of purity and are usually sold at relatively low prices.

The other six chlorophenols are made by five companies that generally manufacture fine or specialty chemicals:

Velsicol Chemical Corp.—Beaumont, Texas
Eastman Kodak Company—Rochester, New York

TABLE 13. 1977 PENTACHLOROPHENOL PRODUCTION CAPACITY[a]

Company	Production location	1977 Capacity (millions of pounds)
Dow Chemical Company[b]	Midland, MI	17
Monsanto Company[c]	Sauget, IL	26
Reichold Chemicals	Tacoma, WA	20
Vulcan Materials Company	Witchita, KN	16
	Total capacity	79

a—Source: American Wood Preservers Institute 1977. These figures presumably do not include production of sodium or potassium salts of pentachlorophenol.

b—Dow ceased production of the sodium salt of PCP (Dowicide G) in April, 1978 (Dow Chemical Company 1978).

c—Monsanto stopped all PCP production as of January 1, 1978 (Dorman 1978).

Aldrich Chemical Co., Inc.—Milwaukee, Wisconsin
Specialty Organics, Inc.—Irwindale, California
R.S.A. Corporation—Ardsley, New York

Products from these manufacturers are often batch-produced under contract with specific industrial customers, sometimes to high standards of purity. They are manufactured in much smaller quantities than those described above, often intermittently, and they are sold at a relatively high price. Often, the products from these companies are used in the manufacture of pharmaceuticals, photographic chemicals, and similar high-quality chemical materials. Without exception, the chlorophenols made by these companies are those not formed preferentially through direct chlorination of phenol.

Any chlorophenol with a chlorine atom at position 2 (ortho to the hydroxyl group) may be a precursor for dioxin formation. Nine of the 11 companies are reported to make at least one chlorophenol of this description. Potential for the occurrence of dioxins is therefore not limited to the manufacture of chlorophenols for pesticide use.

It is not known, however, whether the hydrolysis method, which is especially conducive to dioxin formation, is used to make the lower-volume chlorophenols. In many instances, this method probably is not used because the parent polychlorobenzenes needed for raw materials usually cannot be directly synthesized by conventional chlorination techniques. For production of *m*-chlorophenol in high yields, for example, general chemical references describe a synthesis route that involves chlorination of nitrobenzene, followed by reduction, diazotization, and hydrolysis of the nitrate group (Vinopal, Yamamoto, and Casida 1973). Multistep batch processes of this type are necessary to cause the substituents to attach to the ring at unnatural positions (Kozak 1979). These specialized production methods are not addressed in this report.

The primary chemical producers described above are not the only commercial sources of chlorophenols. Other companies purchase chlorophenols from primary producers, combine them with other ingredients, and market the formulated products. Still others deal only in distribution of the chemicals or chemical mixtures. Most often the trade name of the product changes each time it is bought and sold.

2,4,5-Trichlorophenol

In 1972, hexa-, hepta-, and octachlorodioxins were found at concentrations of 0.5 to 10 ppm in four of six trichlorophenol samples analyzed. Tetrachlorodioxins were not detected (0.5 ppm level of detection). The research report implies that the 2,4,5 isomer of trichlorophenol was being analyzed (Woolson, Thomas, and Ensor 1972).

Also in 1972, another study showed dioxins in trichlorophenols (Firestone et al. 1972). Isomers identified in 2,4,5-trichlorophenol (or its sodium salt) at ppm levels were 2,7-di-, 1,3,6,8-tetra-, 2,3,7,8-tetra-, and pentachlorodioxins. High levels of 2,3,7-trichlorodioxin (93 ppm) and 1,3,6,8-tetrachlorodioxin (49 ppm) were found in the 2,4,6 isomers of trichlorophenol. The investigator analyzed for, but could not detect, mono-, hexa-, hepta-, and octachlorodioxins in these trichlorophenol samples. Data from these two studies are included in Table 11 on page 79.

A U.S. EPA position document on 2,4,5-TCP (U.S. Environmental Protection Agency 1978i) was prepared to accompany the August 2, 1978, *Federal Register* notice of rebuttable presumption against continued registration of 2,4,5-TCP products. The position document gives the following description of the known uses of this chemical:

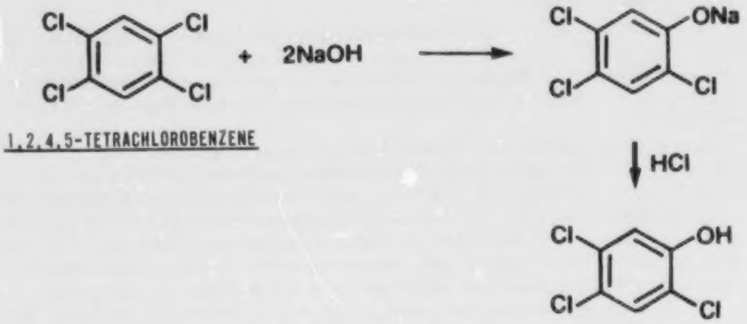
> The largest use of 2,4,5-TCP is as a starting material in the manufacture of a series of industrial and agricultural chemicals, the most notable of which is the herbicide 2,4,5-T and its related products including silvex [2-(2,4,5-trichlorophenoxy) propionic acid], ronnel [0,0-dimethyl 0-(2,4,5-trichlorophenyl)-phosphorothioate], and the bactericide hexachlorophene.
>
> 2,4,5-TCP and its salts are used in the textile industry to preserve emulsions used in rayon spinning and silk yarns, in the adhesive industry to preserve polyvinyl acetate emulsions, in the leather industry as a hide preservative, and in the automotive industry to preserve rubber gaskets. The sodium salt is used as a preservative in adhesives derived from casein, as a constituent of metal cutting fluids and foundry core washes to prevent breakdown and spoilage, as a bactericide/fungicide in recirculating water in cooling towers, and as an algicide/slimicide in the pulp/paper manufacturing industry.
>
> There are some minor uses of 2,4,5-TCP and its salts in disinfectants which are of major importance relative to human exposure. These include use on swimming-pool-related surfaces; household sickroom equipment; food processing plants and equipment; food contact surfaces; hospital rooms; sickroom equipment; and bathrooms (including shower stalls, urinals, floors, and toilet bowls).

It is apparent, therefore, that all the uses of 2,4,5-TCP exploit the poisonous character of the compound and its derivatives. As a pesticide, it is subject to EPA registration in all of its applications except those associated with food processing.

Manufacture—

Only trace amounts of 2,4,5-trichlorophenol are created by direct chlorination of phenol. It can be made in about 50 percent yield by rechlorination of 3,4-dichlorophenol (U.S. Patent Office 1956c). Neither of these production methods is in commercial use in this country.

Domestic commercial production is accomplished through hydrolysis of 1,2,4,5-tetrachlorobenzene, which is a principal isomer produced by rechlorination of *o*-dichlorobenzene. Conversion of this chemical to the sodium salt of 2,4,5-TCP is a batch reaction with caustic soda. Subsequent neutralization with a mineral acid forms the product. The basic process is a typical application of the hydrolysis method of chlorophenol production described earlier. The reaction sequence is given below:



1,2,4,5-TETRACHLOROBENZENE

2,4,5-TRICHLOROPHENOL

At least three variations of the basic process have been described in process patents specifically for production of 2,4,5-TCP, differing only in the solvents used and therefore in the conditions needed to drive the reaction to completion. The first patented process (U.S. Patent Office 1950) uses a solvent of ethylene glycol or propylene glycol at preferred temperatures of 170° to 180° C and pressures up to 20 psi. A second patent, the most recent (U.S. Patent Office 1967b), describes the use of methanol as a solvent, with temperatures ranging from 160° to 220° C and with pressure less than 350 psi (probably 50 to 200 psi). Both of these alcohol-based processes require 1 to 5 hours to complete.

A third patent (U.S. Patent Office 1957b) describes the use of water as the reaction solvent. Use of water necessitates the most severe operating conditions: operating temperatures from 225° to 300° C and pressures from 400 to 1500 psi. This method permits greater production, since reaction time is reduced to no more than 1.5 hours and in some instances to as little as 6 minutes. In addition to its production efficiency, the water-based process eliminates the side reactions between caustic and the alcohol solvents, which form undesired impurity compounds. The process also improves product yield and eliminates solvent costs. It appears, however, that the high-temperature, high-pressure, and strongly alkaline conditions of the water-based process promote a continuation of the reaction, in which 2,4,5-TCP combines with itself to form 2,3,7,8-TCDD (see Figure 13, p. 59).

The patent examples cited above are fairly old, and details of the current 2,4,5-TCP production methods are difficult to obtain. A 1978 EPA report on 2,4,5-TCP briefly describes present-day 2,4,5-TCP manufacture as a reaction of tetrachlorobenzene with caustic in the presence of methanol at 180° C under pressure. Although a final product purification step is described in the most recent patent example (U.S. Patent Office 1967b), the EPA report does not describe it.

A more detailed estimate of current production methods is derived from fragmentary descriptions of both U.S. and foreign operations (Sidwell 1976; World Health Organization 1977; Fuller 1977; Whiteside 1977; Fadiman 1979; D. R. Watkins 1980). (One plant from which much of this information was derived ceased production of 2,4,5-TCP in 1979.) Figure 31 is a flow chart prepared from

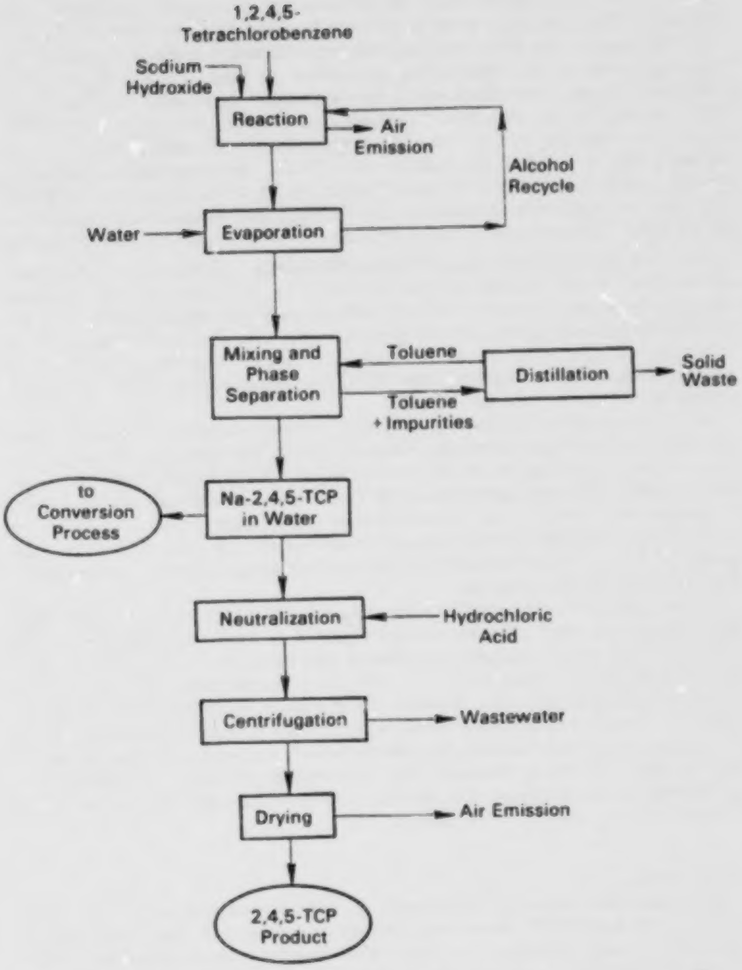


Figure 31. Flow chart for 2,4,5-TCP manufacture.

these sources, showing the most likely process details. In this processing scheme, alcohol and caustic are mixed and heated. Tetrachlorobenzene is added, an exothermic reaction begins, and cooling water is turned onto the reactor coils. After all the tetrachlorobenzene has been added, the batch is "aged"; during the aging period, sodium-2,4,5-trichlorophenate (Na-2,4,5-TCP) is formed. Volatile compounds such as dimethyl ether also are formed during the aging step; these are vented from the reactor, along with small amounts of vaporized methanol. According to Vertac, Inc., dimethyl ether is absorbed by a water scrubber, in which it is highly soluble. The presence of these flammable vapors presents a fire or explosion hazard, and the reaction vessel is usually enclosed in blastproof walls to minimize physical damage from any accident that may occur during the aging step.

On completion of the reaction, the methanol is evaporated, condensed, and recycled. At the same time, water is added to keep the batch contents in solution.

In this process, a toluene washing step is conducted to purify the product by removing some of the high-boiling impurities. Toluene condensed from the overhead of an auxiliary still is mixed into the cooled water solution of Na-2,4,5-TCP. The mixture is then allowed to stand quietly so that the water and organic phases can separate into layers. The organic layer, containing impurities, is decanted and returned to the toluene still as feed. The water layer, containing partially purified Na-2,4,5-TCP, can be used directly to manufacture a herbicide derivative. Alternatively, hydrochloric acid can be added to neutralize the mixture. Acidic 2,4,5-TCP precipitates and is separated from the liquid by centrifugation.

Many of the impurities created during this process, including 2,3,7,8-TCDD, accumulate in the bottom of the toluene still. Still bottoms are removed periodically to be discarded. Toluene still bottoms have been identified as the source of at least one exposure of the public to dioxins, and also as the source of one of the highest concentrations of 2,3,7,8-TCDD (40 ppm) ever discovered in such wastes (Watkins 1979, 1980; Richards 1979a). (Analysis of this waste sample is fully described in Section 4 of this report.)

As shown in Figure 31, the acidic 2,4,5-TCP is dried and either packaged for sale or used to manufacture other derivative products. One reference shows one or more stages of purification of the product after it is centrifuged from the water solution (World Health Organization 1977). One stage of high-vacuum distillation is conducted to create what is described as "agricultural grade 2,4,5-TCP." A second stage of distillation removes additional impurities to form "pharmaceutical grade 2,4,5-TCP." It is believed that all U.S. hexachlorophene is made from a distilled grade of this chemical.

Process details concerning the only remaining 2,4,5-TCP plant in the United States have not been released. It was reported in 1967 that this plant (Dow Chemical Company, Midland, Michigan) was using the water-based process described in its 1955 patent (Sconce 1959; U.S. Patent Office 1957b), but this probably is not the case today. Another report states that the process is conducted with very careful temperature control to prevent the formation of dioxins (Sittig 1974). This source also indicates that still bottoms from the manufacture of 2,4,5-T at this plant are being discarded by incineration; therefore, a distillation is presumably being performed. It is not known whether these still bottoms are from a toluene washing still or from a product still.

Production—

Dow Chemical Company is apparently the only current producer of both 2,4,5-TCP and Na-2,4,5-TCP. Merck and Company has recently begun producing Na-2,4,5-TCP (Stanford Research Institute 1979). Current records related to the EPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) indicate that 42 companies, including Dow, are marketing 94 registered commercial products containing 2,4,5-TCP or its salts (U.S. Environmental Protection Agency 1978i). According to EPA sources, most, if not all, of these companies obtain the basic chemical from Dow (Reece 1978c).

Former 2,4,5-TCP manufacturing sites are listed in Table 14 by location and owner. Details of the processes used by these former producers are not known; however, "still bottoms" were said to be the source that created a dioxin exposure at Verona, Missouri (see Section 5). The methanol-based process with a toluene washing stage was used by Vertac, Inc. (Watkins 1980).

Current U.S. production figures for 2,4,5-TCP and its salts are not available (U.S. Environmental Protection Agency 1978i). In 1970, the estimated level of domestic production for 2,4,5-TCP and its derivatives was 50 million pounds (Crosby, Moilanen, and Wong 1973). In 1974, the reported annual world

TABLE 14. FORMER 2,4,5-TCP MANUFACTURING SITES[a]

Plant location	Owner
Niagara Falls, NY	Hooker Chemicals and Plastics (approximately 45 years)[b]
Jacksonville, AR	Reasor-Hill Corp. (1946-61)[c] Hercules, Inc. (1961-71)[c] Transvaal, Inc. (1971-78)[c]
Verona, MO	North Eastern Pharmaceuticals and Chemicals Co.
Monmouth Junction, NJ	Rhodia, Inc.
Linden, NJ	GAF Corp.
Chicago, IL	Nalco Chemical Co.
Cleveland, OH	Diamond Shamrock Corp.

a—Unless otherwise noted, the information in this table was derived from Stanford Research Institute Directory of Chemical Producers, United States 1976-79, and U.S. International Trade Commission Synthetic Organic Chemicals, U.S. Production and Sales 1968, 1974, 1976-78.

b—Chemical Week 1979a.

c—Richards 1979a.

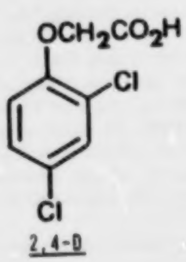
production of all chlorophenols and their salts was estimated to be 100,000 tons, or 200 million pounds (Nilsson et al. 1974).

Chlorophenol Derivatives with Confirmed Dioxin Content

The wide utilization of chlorophenols in chemical synthesis makes it virtually impossible to identify all the potential derivatives of this class of compounds. The following paragraphs outline the manufacture of derivatives that, upon analysis, have been reported to contain chlorinated dioxins. The products are all pesticides, which are usually made as only partially purified chemicals and are intended to be distributed rather broadly into the environment.

2,4-D, 2,4-DB, 2,4-DP, and 2,4-DEP—

The compound 2,4-dichlorophenoxyacetic acid (2,4-D) is a widely used herbicide and a close chemical relative of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) described later in this section. A 50:50 mixture of these two chemicals, known as "Herbicide Orange" (earlier called "Agent Orange"), was used as a defoliant during the Vietnam conflict. The chemical formula of 2,4-D is shown below.



2,4-D

The herbicide 2,4-DB is 4-(2,4-dichlorophenoxy) butyric acid; 2,4-DP is 2-(2,4-dichlorophenoxy) propionic acid; and 2,4-DEP is tris [2 - (2,4-dichlorophenoxy) ethyl] phosphite; all are closely related chemically to 2,4-D.

In 1972, Woolson, Thomas, and Ensor found hexachlorodioxin in one sample of 2,4-D at a level between 0.5 and 10 ppm. No other dioxins were observed. Twenty-three other 2,4-D samples, as well as three 2,4-DB and two 2,4-DEP samples, were analyzed, but no dioxins were found at a 0.5 ppm limit of detection. Apparently, only tetra-, hexa-, hepta-, and octachlorodioxins were sought in these analyses. The samples apparently were not analyzed for dichlorodioxins, which should be more likely to occur (see Figure 17, p. 64).

According to the World Health Organization (1977), 2,4-D is widely used as a herbicide for broadleaf weed control in cereal crops (wheat, corn, grain sorghum, rice, other small grains), sugar cane, and citrus fruits (lemons), and on turf, pastures, and noncrop land. Food-related uses account for 58 percent of all 2,4-D used in the United States in 1975.

Two manufacturing processes have been described for 2,4-D, only one of which starts with a chlorinated phenol. One process is a direct chlorination of phenoxyacetic acid (U.S. Patent Office 1949). The other process is a reaction between 2,4-dichlorophenol and chloroacetic acid (U.S. Patent Office 1958a). The second process is similar to the 2,4,5-T manufacturing process described in the following section and is also similar to the process used to make 2,4-DB (U.S. Patent Office 1963).

Since many companies make 2,4-D and its esters and salts, both production processes may be in use, although it is claimed that chlorination of phenoxyacetic acid produces a higher yield and is a simpler process. In a batch reactor, phenoxyacetic acid is melted by heating it to 100° C. With continuous agitation, chlorine is bubbled through the molten chemical and the temperature is increased slowly to 150°C. A stream of dry air is passed through the reactor to sweep away the hydrogen chloride byproduct. When the calculated amount of chlorine has been added, the resulting mass is cooled, pulverized, and packaged. No solvent is used, no special recovery operation is needed, and product purification is unnecessary. If dioxins are created during this process, the mechanism of their formation is unknown.

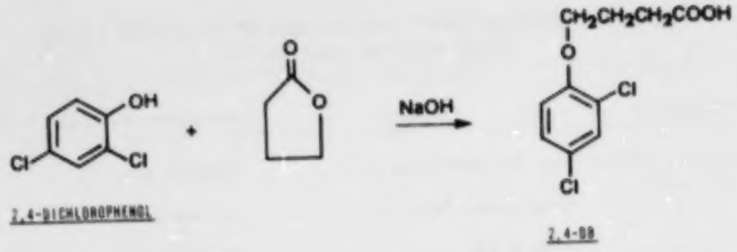
The second process involves reaction of 2,4-dichlorophenol with chloroacetic acid in a solvent mixture of water and sodium hydroxide. This process is said to be used by at least one large manufacturer (Sittig 1974). Heat is applied to the vessel, and the water is evaporated from the mixture. When the temperature begins to rise, indicating that most of the water has evaporated, heating is stopped and a fresh charge of cold acidified water is added. The product can be filtered from the mixture and dried; this procedure would form an impure product.

Alternatively, the product can be extracted from the cooled mixture with a water-immiscible solvent and then separated from the solvent by distillation. This latter recovery method would probably create anhydrous organic wastes and therefore is probably in use by at least one company that has been reported to incinerate waste tars from 2,4-D manufacture (Sittig 1974).

This chlorophenol-based process for making 2,4-D could create dioxins because it provides for an alkaline mixture of a dioxin precursor chemical in contact with hot heating surfaces. If the product is only filtered from the reaction mixture, the dioxin contaminants would be captured along with the product. If solvent extraction is employed, part of the dioxin would probably appear in wastes from the process and part would probably be captured with the product.

The process for manufacture of 2,4-DB uses 2,4-dichlorophenol and gamma butyrolactone in a solvent mixture of dry butanol and nonane, with sodium hydroxide as a reaction aid. The chemical reactions are shown on the following page.

The ingredients are mixed and heated to a temperature of about 165° C for a



period that may range from 1 to 24 hours. On completion of the reaction, dilute sulfuric acid is added and 2,4-DB precipitates; the precipitate is centrifuged from the mixtures, dried, and packaged. Liquids from the centrifuge are allowed to stand quietly and separate into two liquid layers. The water fraction is discarded, and the organic layer is recycled to the subsequent reaction batch. Any water that is brought into the reactor is removed by distillation before the next reaction is started.

It is possible that dioxins could be produced by this process by the mixture of 2,4-dichlorophenol with sodium hydroxide being brought into contact with a hot surface (see Figure 18, p. 65). Product recovery methods are such that any dioxins formed would either be removed as solids along with the product or be recycled to the succeeding batch.

Commercial production of 2,4-D in the United States started in 1944 and by the mid-1960's had peaked at 36 million kg (World Health Organization 1977). After the use of Herbicide Orange was discontinued, production dropped. Production in 1974 is estimated to have been 27 million kg (World Health Organization 1977). Production figures for 2,4-DB and 2,4-DEP are not available.

The current basic producers of 2,4-D and 2,4-DB acids, esters, and salts as reported by Stanford Research Institute in 1978 are listed in Table 15. Former producers or production sites are listed in Table 16. No current producers of 2,4-DEP are listed in the Stanford Research Institute publication of 1978.

Sesone—

The chemical name for the pesticide sesone is 2-(2,4-dichlorophenoxy) ethyl sodium sulfate. The only sample known to have been analyzed for dioxins contained 0.5 to 10 ppm hexachlorodioxin (Helling et al. 1973). No tetra-, hepta-, or octachlorodioxins were detected (0.5 ppm detection level). Analysis apparently was not performed for di-, tri-, or pentachlorodioxins.

Sesone is made from 2,4-dichlorophenol by boiling it for several hours in a water solution of beta-chloroethyl-sodium sulfate and sodium hydroxide. The following are the chemical reactions of the process:

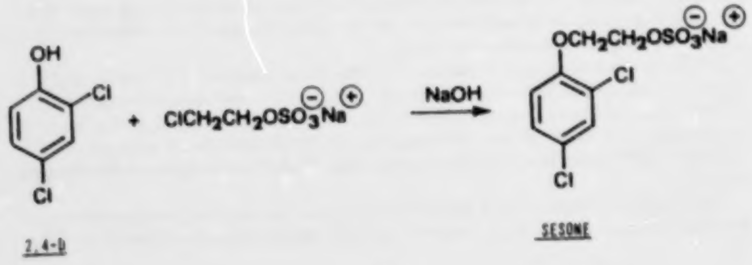

OH
Cl
Cl
$ClCH_2CH_2OSO_3^{\ominus}Na^{\oplus}$
NaOH
$OCH_2CH_2OSO_3^{\ominus}Na^{\oplus}$
Cl
Cl
2,4-D
SESONE

TABLE 15. CURRENT BASIC PRODUCERS OF 2,4-D AND 2,4-DB ACIDS, ESTERS, AND SALTS[a]

Pesticide	Company	Production location
2,4-D and esters and salts	Dow Chemical Company	Midland, MI
	Fallek-Lankro Corp.	Tuscaloosa, AL
	Imperial, Inc.	Shenandoah, IA
	North American Phillips Corp., Thompson-Hayward Chemical Co., subsidiary	Kansas City, KS
	PBI-Gordon Corp.	Kansas City, KS
	Rhodia, Inc.	Portland, OR St. Joseph, MO Chicago Heights, IL
	Riverdale Chemical Co.	Chicago Heights, IL
	Union Carbide Corp., Amchem Products, Inc., subsidiary	Ambler, PA Fremont, CA
	Vertac, Inc., Transvaal, Inc., subsidiary	Jacksonville, AR
2,4-DB and salts	Rhodia, Inc.	Portland, OR
	Union Carbide Corp., Amchem Products, Inc., subsidiary	Ambler, PA

a—Source: Stanford Research Institute 1978.

In more detail, the straight-chain reactant is made by combining ethylene chlorohydrin and chlorosulfonic acid in a refrigerated water solution (U.S. Patent Office 1958c). After partial neutralization with sodium hydroxide, 2,4-dichlorophenol is added and the mixture is boiled for about 15 hours. According to the patent example, the mixture is probably not purified; it is simply spray-dried to form a usable product. It could be purified by repeated extractions with hot alcohol to separate the sodium sulfate impurity.

The manufacture of sesone meets all of the requirements for promotion of the formation of 2,7-DCDD (see Figure 16, p. 62). Both the raw material and the final product contain a chlorine atom ortho to a ring-connected oxygen atom, and the mixture is heated in the presence of sodium hydroxide. Although overall reaction temperature is only slightly above 100° C, it could be higher at the heating surfaces.

The volume of sesone produced annually is not known. Only nine commercial products containing the herbicide are currently registered as pesticides with EPA.

TABLE 16. FORMER BASIC PRODUCERS OF 2,4-D AND 2,4-DB ACIDS, ESTERS, AND SALTS[a]

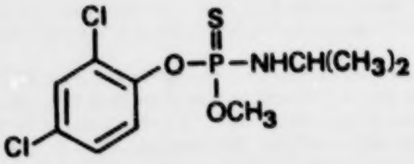
Pesticide formerly reported produced	Company	Production location
2,4-D acid, esters, and salts	Chempar	Portland, OR
	Miller Chemical, subsidiary of Alco Standards	Whiteford, MD
	Rhodia, Inc.	North Kansas City, KS St. Paul/Minneapolis, MN
	Thompson Chemical	St. Louis, MO
	Woodbury, subsidiary of Comutrix	Orlando, FL
2,4-DB and salts	Rhodia, Inc.	North Kansas City, MO St. Paul/Minneapolis, MN

a—Source: Dryden et al. 1980.

DMPA—

The chemical name for DMPA is 0-(2,4-dichlorophenyl) 0-methyl isopropylphosphoramidothioate (Merck Index 1978). Some of the relatively higher chlorodioxins (hexa-, hepta-, and/or octachlorodioxins) were detected at ppm levels in at least one DMPA sample analyzed in 1972 (Helling et al. 1973).

The following is the structure for DMPA.



DMPA

Synthesis of this molecule involves the methanolysis of 0-(2,4-dichlorophenyl) phosphorodichloridothioate, which is made through the phosphoralation of dichlorophenol (U.S. Patent Office 1960; Blair, Kaner, and Kenaga 1963).

DMPA is known commercially as Zytron, K-22023, and Dow 1329 (Merck Index 1978). It is useful as an insecticide, especially against houseflies (Blair, Kaner, and Kenaga 1963). It is also useful as a herbicide for controlling the growth of undesirable plants (U.S. Patent Office 1963; Merck Index 1978). DMPA is not believed to be produced in large amounts. Currently three companies—Dow

Chemical Company, Techne Corp., and Rhodia Chemical Company—have each registered one DMPA pesticide product with EPA (U.S. Environmental Protection Agency 1978f).

Trichlorophenol Derivatives—

As mentioned earlier, the largest use of 2,4,5-TCP is as a starting material in the manufacture of several pesticide and bactericide products. Table 17 lists the known 2,4,5-TCP derivatives, their specific uses, and the companies which have recently been reported to produce them.

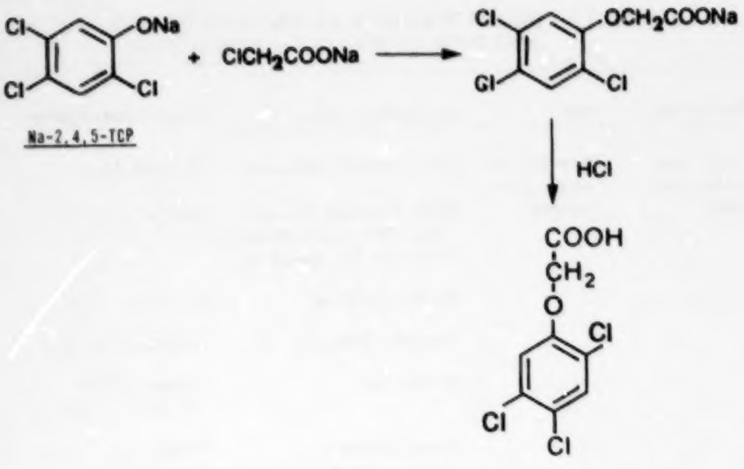
2,4,5-T—The chemical name for 2,4,5-T is 2,4,5-trichlorophenoxyacetic acid and it is the most important derivative of 2,4,5-trichlorophenol. It has been a registered pesticide for about 30 years (U.S. Environmental Protection Agency 1978h) and was used primarily as a herbicide for controlling woody plant growth. 2,4,5-T is best known for its combined use with 2,4-D as Herbicide Orange, which was used extensively by the U.S. military as a defoliant during the Vietnam conflict. When the toxicity of this formulation became apparent, the government suspended all further military use of Herbicide Orange, and in 1970 stopped many registered domestic uses including application to lakes, ponds, ditch banks, homesites, recreational areas, and most food crops (World Health Organization 1977). Until 1979, domestic commercial use of 2,4,5-T continued for control of brush and other hardwood in forestry management and on power transmission right-of-ways, rangelands, rice fields, and turfs. Most of these uses have now been suspended (Blum 1979).

Parts-per-million quantities of dioxins have been reported in 2,4,5-T since 1970 (World Health Organization 1977). A study (Woolson, Thomas, and Ensor 1972; Kearney et al. 1973b; Helling et al. 1973) of samples manufactured between 1950 and 1970 found 0.5 to 10 ppm TCDD's in 7 of 42 samples tested; another 13 samples contained 10 to 100 ppm TCDD's. Hexa-CDD's were found in 4 of the 42 samples. The limit of detection in this study was reported as 0.5 ppm for each dioxin. Most samples came from a company that no longer produces 2,4,5-T. Elvidge (1971) reported that five of six 2,4,5-T samples contained TCDD's at levels ranging from 0.1 to 0.5 ppm. The dioxin was present in two 2,4,5-T ester samples at 0.2 to 0.3 ppm. TCDD's were also found in two 2,4,5-T ester formulations at 0.1 and 0.2 ppm. The level of detection was 0.05 ppm. Storherr et al. (1971) reported finding 0.1 to 55 ppm TCDD's in seven of eight samples of technical 2,4,5-T (see Figure 13, p. 59).

Analysis of 200 samples of Herbicide Orange for TCDD's by the U.S. Air Force showed 0.5 ppm or less in 136 samples and more than 0.5 ppm in the remainder. The highest level was 47 ppm (Kearney et al. 1973). Early in 1976, investigators at Wright State Univeristy analyzed 264 samples of U.S. Air Force stocks of Herbicide Orange and found TCDD's at levels ranging from 0.02 to 54 ppm (Tiernan 1975). The level of detection was 0.02 ppm.

2,4,5-T with a TCDD isomer content of less than 0.1 ppm is now commercially available from U.S. producers (U.S. Environmental Protection Agency 1978h). Commercial 2,4,5-T guaranteed to contain less than 0.05 ppm TCDD's is available from foreign producers (World Health Organization 1977).

The commercial method of producing 2,4,5-T is briefly described in EPA Position Document 1 (April 1978) on this pesticide (U.S. Environmental Protection Agency 1978h). According to this document, 2,4,5-TCP is reacted with chloroacetic acid under alkaline conditions. Subsequent addition of sulfuric acid produces 2,4,5-T (acidic form), which can then be reacted with a variety of alcohols or amines to produce 2,4,5-T esters and amine salts. The chemical reactions are as follows:



Na-2,4,5-TCP

2,4,5-T

A more complete description of the 2,4,5-T production process appears in a patent record (U.S. Patent Office 1958a). Sodium 2,4,5-trichlorophenate is most often delivered to the process as a water solution containing excess sodium hydroxide directly from the Na-2,4,5-TCP manufacturing process. Amyl or isoamyl alcohol, or a mixture of these solvents, is added, and heat is applied to remove water as an azeotrope. When all water has been removed, chloroacetic acid is added to initiate the reaction that produces sodium 2,4,5-trichlorophenoxyacetate (Na-2,4,5-T) and sodium chloride. The reaction proceeds under total reflux for about 1.5 hours at 110° to 130° C and atmospheric pressure. An excess of sodium hydroxide is present during the reaction.

Water is then fed into the reactor and distillation is resumed, this time to remove the amyl alcohol and replace it with water. At the end of the second distillation, the reaction mixture consists of Na-2,4,5-T dissolved in a sodium chloride brine.

The patent example incorporates a purificiation step that may not be conducted in commercial practice. Near the end of the second distillation, activated carbon may be added to adsorb heavy or colored impurities, which would include dioxins that were present in the Na-2,4,5-TCP feedstock. On completion of the second distillation, the carbon would be filtered from the mixture and discarded. If this step is conducted, the process will generate a waste carbon sludge likely to be contaminated with dioxins. If this step is not conducted, any dioxins present are likely to be carried through the process and appear in the final product.

In either variation, the next step is to add acid to neutralize the residual caustic and to form insoluble 2,4,5-T. The product is then filtered or centrifuged from the waste brine, dried, and packaged for sale. The filtrate from this step should contain only soluble sodium chloride and sulfate, excess neutralization acid, and very small quantities of organic matter; it is discarded as a liquid waste.

The patent that describes the manufacture of 2,4,5-T is unusually detailed and indicates that the temperature during the process is never above 140° C, which is lower than the temperature believed to be necessary to create dioxins. Any dioxins that enter with the feed will appear either in the product or in process wastes, but additional dioxins probably are not formed during 2,4,5-T manufacture. Even during abnormal operation or an industrial fire, it would be difficult for the temperature to exceed by far the low boiling point of amyl alcohol, since all operations take place in unpressurized vessels.

TABLE 17. DERIVATIVES OF 2,4,5-TRICHLOROPHENOL AND THEIR RECENT (1978) PRODUCERS[a]

Derivative	Use	Current producers	Production location
2,4,5-T and esters and salts	Herbicide for woody plant control	Dow Chemical Company	Midland, MI
		North American Phillips Corp., Thompson-Hayward Chemical Co., subsidiary	Kansas City, KS
		PBI-Gordon Corp.	Kansas City, KS
		Riverdale Chemical Co.	Chicago Heights, IL
		Rhodia, Inc.[b]	Portland, OR or St. Joseph, MO
		Union Carbide Corp., Amchem Products, Inc., subsidiary	Ambler, PA Fremont, CA St. Joseph, MO
		Vertac, Inc., Transvaal, Inc., subsidiary[c]	Jacksonville, AR
Silvex and esters and salts (Fenoprop)	Herbicide for woody plant control; plant hormone	Dow Chemical Company	Midland, MI
		North American Phillips Corp., Thompson-Hayward Chemical Co., subsidiary	Kansas City, KS
		Riverdale Chemical Co.	Chicago Heights, IL
		Vertac, Inc., Transvaal, Inc., subsidiary[c]	Jacksonville, AR
Erbon	Herbicide, weed and grass killer	Dow Chemical Company[d]	Midland, MI
Ronnel (Fenchlorfos)	Insecticide	Dow Chemical Company	Midland, MI
Hexachlorophene	Bactericide	Givaudan Corporation	Clifton, NJ

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[a] Source: 1978 Directory of Chemical Producers, United States.

[b] Rhodia is not listed in the 1978 Directory of Chemical Producers, United States, but has been recently cited by the EPA (Blum 1979) and the news media (Wall Street Journal 1979 and Environmental Reporter 1979a) as a manufacturer of 2,4,5-T.

[c] In 1979 this company ceased production of 2,4,5-trichlorophenol for subsequent conversion to 2,4,5-T and silvex.

[d] Although erbon is not listed in the 1978 Directory of Chemical Producers, United States, several companies including Dow Chemical Company have registered erbon pesticide products with the EPA. Dow is most likely the basic producer of the herbicide.

The highest production of 2,4,5-T occurred between 1960 and 1968, when it peaked at 16 million pounds per year (World Health Organization 1977). Between 1960 and 1970 a total of 106.3 million pounds was produced domestically (Kearney et al. 1973b). Production declined during the 1970's because of restrictions on use of the compound. In 1978 the annual U.S. usage of 2,4,5-T was estimated at only 5 million pounds (American Broadcasting Co. 1978). Because of EPA's March 1979 emergency ban on most of the remaining uses (Blum 1979), current usage is believed to be even less, probably less than 2 million pounds per year.

2,4,5-T may be produced and formulated in several forms as salts and esters of the acid. The low-volatility esters have been used most often. Emulsifiable concentrates of 2,4,5-T salts and esters contain 2 to 6 pounds per gallon of the acid equivalent; oil-soluble concentrates contain 4 to 6 pounds of active ingredient per gallon (U.S. Environmental Protection Agency 1978h).

Until 1979, this herbicide was probably produced by the seven companies shown in Table 18. Over a hundred companies were recently marketing more than 400 formulated pesticide products containing 2,4,5-T (U.S. Environmental Protection Agency 1978h).

TABLE 18. FORMER PRODUCERS OF 2,4,5-T
(Prior to 1978)[a]

Company	Location
Chempar	Portland, OR
Diamond Shamrock Corp.	Cleveland, OH
Hoffman-Taft, Inc.	Springfield, MO
Hercules, Inc.	Wilmington, DE
Monsanto Company	St. Louis, MO
Rorer-Amchem	Ambler, PA Fremont, CA St. Joseph, MO Jacksonville, AR
Wm. T. Thompson Company, Thompson Chemical Division	St. Louis, MO

a—Sources: Stanford Research Institute Directory of Chemical Producers, United States 1976 and 1977. United States Tariff Commission/United States International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales 1968, 1974, 1976, and 1977.

Silvex—Silvex is a family of compounds that act as hormones to plants and can be used as specific herbicides. Formulations containing these materials were used for control of woody plants on uncropped land and for control of weeds on residential lawns until 1979, when sales of most products containing silvex were halted (Blum 1979). Silvex is still being used on noncrop areas, on rangelands and orchards, and on rice and sugar cane (Toxic Materials News 1979b; Chemical Regulation Reporter 1979c).

The chemical name for silvex acid is 2-(2,4,5-trichlorophenoxy) propionic acid. It is also known as Fenoprop, 2,4,5-TP, and 2,4,5-TCPPA.

Silvex is available either as the acid or esters and salts of the acid. The low-volatility esters are probably the form most widely used.

TCDD's were detected (1.4 ppm) in one of seven silvex samples manufactured between 1965 and 1970 and analyzed in 1972; no other dioxins were detected (Woolson, Thomas, and Ensor 1972; Kearney et al. 1973b).

The following are recent producers of silvex as listed in the 1978 Stanford Research Institute Directory of Chemical Producers:

Dow Chemical Company—Midland, Michigan

North American Phillips, Thompson Hayward Chemical, subsidiary—Kansas City, Kansas

Riverdale Chemical—Chicago Heights, Illinois

Vertac, Inc., Transvaal, Inc., subsidiary—Jacksonville, Arkansas

Hercules, Inc., of Wilmington, Delaware, is a former producer (U.S. Tariff Commission 1968). The 1978 EPA pesticide files indicate that more than 300 products or formulations containing silvex are registered (U.S. Environmental Protection Agency 1978f).

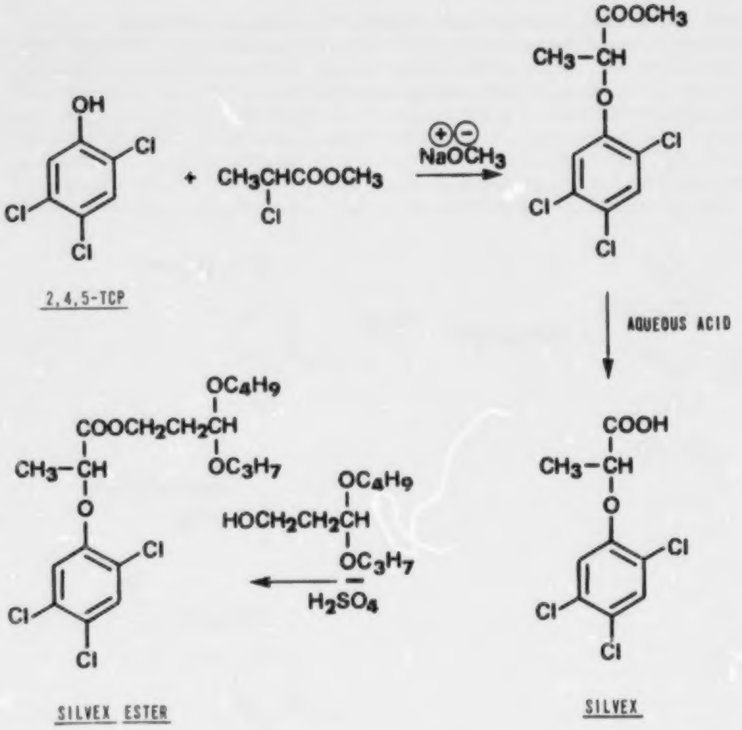
Silvex manufacture is more complex than that of other 2,4,5-TCP derivatives. The compounds sold commercially are usually complex esters, made from a specialized alcohol and silvex acid. The final manufacture of the ester is well documented in a process patent (U.S. Patent Office 1956a), as is the manufacture of the specialized alcohol. No definitive information has been found, however, on manufacture of the silvex acid, probably because compounds of this type can be manufactured by a long-established chemical reaction that is used in many categories of the organic chemical industry (J. Am. Chem. Soc. 1960). Silvex acid would be the source of any dioxins in commercial silvex products (see Figure 14, p. 60). The figure on the following page illustrates the most likely chemical reaction that would form the silvex acid and also shows the subsequent esterification, as described in the patent.

In the first step, 2,4,5-TCP is probably brought into reaction with the methyl ester of 2-chloropropionic acid, with methanol as the solvent and sodium methoxide as a reaction aid. This reaction would occur approximately at the boiling temperature of methanol, which is 65° C. The resulting compound would probably be separated from the reaction mixture by treatment with acidified water followed by extraction with a chlorinated hydrocarbon.

The addition of more acidified water to the extractant and a subsequent evaporation at a temperature near 100° C would hydrolyze the intermediate compound and also would drive off the chlorinated hydrocarbon for recycle and the methanol byproduct to be reclaimed for other uses. The resulting compound is 2-(2,4,5-trichlorophenoxy) propionic acid, which is known to be a reactant in the subsequent processing (U.S. Patent Office 1956a).

Other methods could be used to prepare this intermediate acid, but none of them would utilize high temperatures or unusual solvents. The use of a strongly alkaline hydrolysis step, rather than an acidic medium, is possible. In any method, the last step is probably another solvent extraction using 1,2-dichloroethane to prepare the mixture for the next operation.

Silvex acid can be converted to various esters by using selected ether alcohols. The esterification steps are identical except for variations in the alcohol raw material. In a solvent of 1,2-dichloroethane, with concentrated sulfuric acid as a reaction aid, the intermediate acid is mixed with an ether alcohol. In the following example, butoxypropoxypropanol is used. The mixture is held at about 95°C for about 7 hours. During this period, the water formed in the reaction is removed by passing the reflux condensate through a decanter. At the end of the reaction, the product is present as an insoluble precipitate, which is filtered from the mixture, washed with sodium carbonate solution, and vacuum-dried at about 90° C.



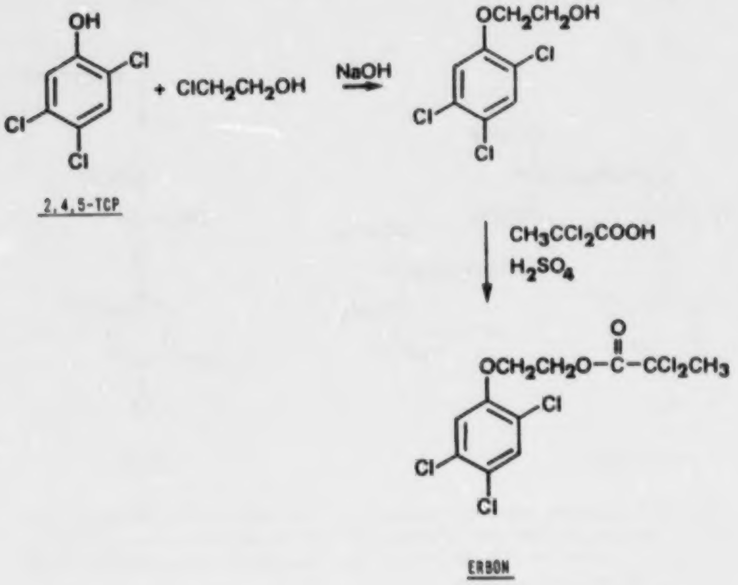
Although complete data are unavailable, no information indicates that temperatures greater than 100° C would occur at any step in the manufacture of acidic silvex or its esters. It is therefore unlikely that dioxin compounds would be created as side reaction products.

Absence of detailed information makes it impossible to establish whether dioxin contamination would carry through from the 2,4,5-TCP raw material into the final product. Theoretical considerations do not permit an estimation of the degree of purification required by the various intermediate compounds. Probably, as noted above, at least two solvent extraction operations are used to separate the principal processing materials from water solutions. Since TCDD's are very slightly soluble in chlorinated organic solvents, some could be carried through these operations, but most should be rejected.

Erbon—Very little information is available on erbon, which is derived from 2,4,5-trichlorophenol. Analysis of one erbon sample produced in 1970 indicated more than 10 ppm octachlorodioxin (Woolson, Thomas, and Ensor 1972). Tetra-, penta-hexa-, and heptachlorodioxins were not detected (0.5 ppm limit of detection).

In 1978, nine companies had registered 17 products containing erbon (U.S. Environmental Protection Agency 1978). Dow is probably the only producer of the basic chemical. The other companies are most likely formulators who obtain their basic erbon ingredient from Dow. The volume of erbon produced annually is not known.

This herbicide is an ester based on 2,4,5-TCP. Although the initial manufacturing step is not reported, the first intermediate is almost identical to that used to make sesin. General organic chemical references indicate that it is probably made by an initial reaction of 2,4,5-TCP with ethylene chlorohydrin (March 1968). Water is the most likely solvent, made strongly alkaline with sodium hydroxide, and the intermediate probably precipitates on addition of acid and is filtered from the solution and dried. A process patent (U.S. Patent Office 1956b) discloses that the second reaction step is a combination of the intermediate with 2,2-dichloropropionic acid in a solution of ethylene dichloride (1,2-dichloroethane), with addition of a small amount of concentrated sulfuric acid to remove the water formed in the reaction. These chemical reactions are shown by the following sequence drawing:



The resulting reaction mixture is partially purified by washing with water and is then fractionally distilled under vacuum to recover ethylene dichloride for recycle and possibly to separate the product from any impurities.

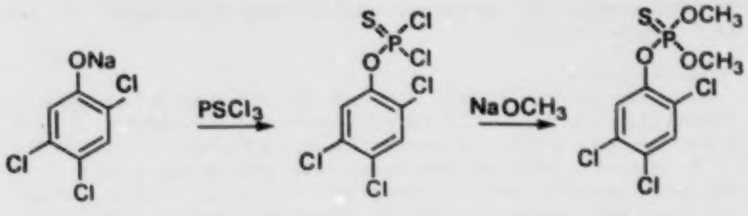
The first step of the reaction is the one that could possibly form dioxins (see Figure 16, p. 62). Both the raw material and the resulting intermediate contain a chlorine atom ortho to a ring-connected oxygen atom, and the mixture is heated with sodium hydroxide. Temperatures are not high, however, since water is probably the solvent used and this simple reaction ordinarily does not require application of pressure. Dioxin formation could occur at the surface of steam coils if high-pressure steam is used for distillation.

Apparently no operation other than the final distillation would remove any dioxin contamination from this material. Since the most likely impurities would be more volatile than the final ester, even the distillation may not serve to isolate dioxins into a waste stream. Most dioxins either formed by the process or present in the raw material would probably be collected with the final product.

Ronnel—The chemical name of ronnel is 0,0-dimethyl 0-(2,4,5-trichlorophenyl) phosphoroate. This insecticide is also known by such names as fenchlorfos, Trolene, Etrolene, Nankor, Korlan, Viozene, and Ectoral (Merck Index 1978).

Ronnel is effective in the control of roaches, flies, screw worms, and cattle grubs (Merck Index 1978). In 1972, highly chlorinated dioxins were detected at ppm levels in an unknown number of ronnel samples (Woolson, Thomas, and Ensor 1972).

The manufacture of ronnel is a two-step process (U.S. Patent Office 1952) in which Na-2,4,5-TCP is reacted first with thiophosphoryl chloride, then with sodium methoxide. The chemical reactions are shown below:



Na-2,4,5-TCP

RONNEL

In the first step, dry Na-2,4,5-TCP is added to an excess of thiophosphoryl chloride (2 to 4 times the theoretical amount) and heated slightly, perhaps to 80° C. Sodium chloride is formed as an insoluble precipitate; it is filtered from the mixture and discarded. The clear filtrate is vacuum-distilled to recover the excess thiophosphoryl chloride for recycle and to fractionally separate the intermediate from side reaction impurities.

In a separate reaction vessel, metallic sodium is mixed with methanol. Hydrogen gas is liberated, creating a methanolic solution of sodium methoxide. This solution is mixed slowly with the purified intermediate while the mixture is maintained at approximately room temperature with noncontact cooling water.

When measured amounts of both reactants have been combined, the mixture is held for a period of time to ensure completion of the reaction. A nonreactive organic solvent is then used to extract the product from a mixture of methanol, excess sodium methoxide, and byproduct sodium chloride. Suitable extraction solvents are carbon tetrachloride, methylene dichloride, and diethyl ether. The extraction solvent is decanted from the mixture, washed with water solutions of sodium hydroxide, and fractionally vacuum-distilled to separate the extraction solvent for recycle and to separate ronnel from side reaction byproducts.

Throughout this process, the temperature probably does not exceed 150° C. The highest temperature probably occurs in the base of the final distillation column. In theory, additional dioxins are not likely to be created by this process because of the absence of high temperature and pressure, although all other conditions meet the requirements for formation of 2,3,7,8-TCDD (see Figure 15, p. 61).

It appears even less likely that dioxins originally present in the Na-2,4,5-TCP raw material would be carried through into the product. If all the steps outlined above are properly conducted, some of the operations might isolate dioxins into waste streams. The solubility of dioxins in thiophosphoryl chloride is unknown; if they are insoluble, they would be removed with the first filtration. Because the solubility of dioxins in chlorinated methanes is very slight (0.37 g/liter for TCDD in chloroform), much of the dioxin present would not be captured by the extraction solvent and would be carried away with the methanol reaction solvent. Distillations afford two other opportunities to isolate dioxin contaminants into waste organic fractions. Although the probability of dioxins carrying through into the final product appears slight, definitive information is not recorded.

Ronnel is reportedly produced by only one company—Dow Chemical Company, Midland, Michigan (Stanford Research Institute 1978). Annual production volume is not known. It is found in over 300 pesticide formulations registered by more than 100 companies.

Chlorophenol Derivatives with Unconfirmed Dioxin Content

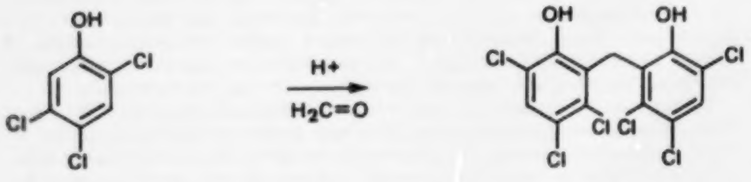
This subsection deals with several other chlorophenol derivatives that may contain dioxins. The compounds discussed include those that have been analyzed for dioxin content with negative results and also those for which analytical data have not been reported.

Hexachlorophene—

Hexachlorophene is known chemically as either bis-(3,4,6-trichloro-2-hydroxyphenyl) methane, or 2,2'-methylene-bis (3,4,6-trichlorophenol). It is also known commercially as G-11 (Cosmetic, Toiletry, and Fragrance Association, Inc. 1977). Hexachlorophene is an effective bactericide and fungicide. Prior to 1972 it was widely advertised and distributed as an active constituent of popular skin cleansers, soaps, shampoos, deodorants, creams, and toothpastes (Wade 1971; U.S. Dept. HEW 1978). Although its use has been considerably restricted by the Food and Drug Administration, it still may be used as a preservative for cosmetics and over-the-counter drugs; the concentration is restricted to 0.1 percent in these products. Skin cleansers containing higher levels may also be sold but only as ethical pharmaceuticals, available by medical prescriptions (U.S. Code of Federal Regulations Title 21 1978). As an agricultural pesticide, hexachlorophene is a constituent of formulations used on three vegetables and on some ornamental plants for control of mildew and bacterial spot. It is also used in limited industrial and household applications as a disinfectant.

The grade of hexachlorophene produced today is reported to contain less than 15 μg/kg (< 15ppb) 2,3,7,8-TCDD (World Health Organization 1977). In a 1972 analysis, dioxins could not be detected in hexachlorophene at a detection limit of 0.5 mg/kg (0.5 ppm) (Helling et al. 1973).

Four process patents have been issued on manufacture of hexachlorophene, and all are variations of the following chemical reaction:



2,4,5-TCP

HEXACHLOROPHENE

Hexachlorophene is formed by reacting one molecule of formaldehyde with two molecules of 2,4,5-TCP at elevated temperatures in the presence of an acid catalyst (Moye 1972). The patented processes differ in temperature, reaction time, order of reagent additions, reaction solvents, and other physical parameters.

In the first process, patented in 1941, methanol is the solvent and large amounts of concentrated sulfuric acid are used to bind the water that is formed as a reaction byproduct; the process takes place at 0° to 5° C over a 24-hour period (U.S. Patent Office 1941). A second patent issued in 1948 discloses that the methanol solvent is eliminated and the reaction is conducted with paraformaldehyde at an elevated temperature (135° C) over a 30-minute period (U.S. Patent Office 1948). A 1957 patent reintroduces a solvent, which is one of several chlorinated hydrocarbons (U.S. Patent Office 1957d). Temperature is 50° to 100° C, and reaction time is 2 to 3 hours. Oleum (sulfuric acid plus SO_3) is used as the catalyst and concentrated sulfuric acid is recovered as the byproduct. Finally, a 1971 patent revises the order of reagent addition and also emphasizes the chemical reaction mechanism (U.S. Patent Office 1971). This last-mentioned process is probably the one in present use; its processing sequence is shown in Figure 32.

Patent information indicates that older manufacturing methods probably reclaimed the product from the reaction mixture by neutralizing the sulfuric acid with sodium hydroxide, which would have created a rather large amount of brine waste. In modern processes, conditions are probably maintained so that the residual sulfuric acid separates as a distinct liquid layer when agitation of the mixture is stopped after completion of the reaction. This acid, which contains the water formed during the reaction, is decanted from the mixture; it is strong enough to be used elsewhere in the plant complex, although it probably cannot be used in subsequent hexachlorophene batches.

In the patent examples, the organic layer that remains after the acid is removed is mixed with activated carbon, which is then filtered from solution. The purpose of this treatment is to remove colored impurities. The clear filtrate is then chilled to approximately 0° C; crystals of hexachlorophene precipitate and are filtered from solution, dried, and packaged. The filtrate, which would contain some hexachlorophene, is probably directly recycled for use in succeeding batches.

There is no indication that dioxins would be formed during the production of hexachlorophene, since highly acidic conditions are maintained throughout the process and temperatures are well below those known to be needed for dioxin reactions (Kimbrough 1974). If dioxins are found in hexachlorophene, the most likely explanation for their presence is that contamination in the 2,4,5-TCP raw material is carried through into the final product (see Figure 27, p.74). In a situation identical to that of the 2,4,5-T process, the patent descriptions show the possibility of activated carbon adsorption, which could cause accumulation of dioxins into an extremely hazardous waste. If carbon adsorption is not used in commercial practice or if it is not totally effective, any dioxins in the raw material will either appear in the hexachlorophene product or be recycled to succeeding batches. Although dioxins are not known to be soluble in sulfuric acid, they might be carried out of the process with the acid byproduct; if this were the case, dioxins could then appear in other products of the plant in which the sulfuric acid is utilized.

Givaudan Corporation in Clifton, New Jersey, is apparently the only active U.S. producer of hexachlorophene. Until 1976, the 2,4,5-TCP for hexachlorophene manufacture was produced by Givaudan's ICMESA plant in Seveso, Italy, and shipped to New Jersey for conversion. In 1976, Wright State University analyzed two representative samples of this trichlorophenol and found 1.8 and 1.9 ppb TCDD's (Tiernan 1976). An accident in 1976 closed the ICMESA plant and eliminated Givaudan's primary supply of 2,4,5-TCP. (For further details of the ICMESA incident see Section 5, p. 168). It is now believed that all the 2,4,5-TCP for hexachlorophene manufacture is supplied by Dow Chemical Company and that Givaudan specifies an extremely low dioxin content. In 1978, five waste samples from the Clifton plant were analyzed for chlorinated dioxins. None were found at a 0.1 ppm level of detection (U.S. Environmental Protection Agency 1978d). Subsequent analysis of three of these samples found no TCDD's at 0.1 or less ppb (see Section 4 of this report).

About 400 commercial products containing hexachlorophene have been marketed recently in pesticide, drug, cosmetic, and other germicidal formulations. The annual production volume of the germicide is not reported.

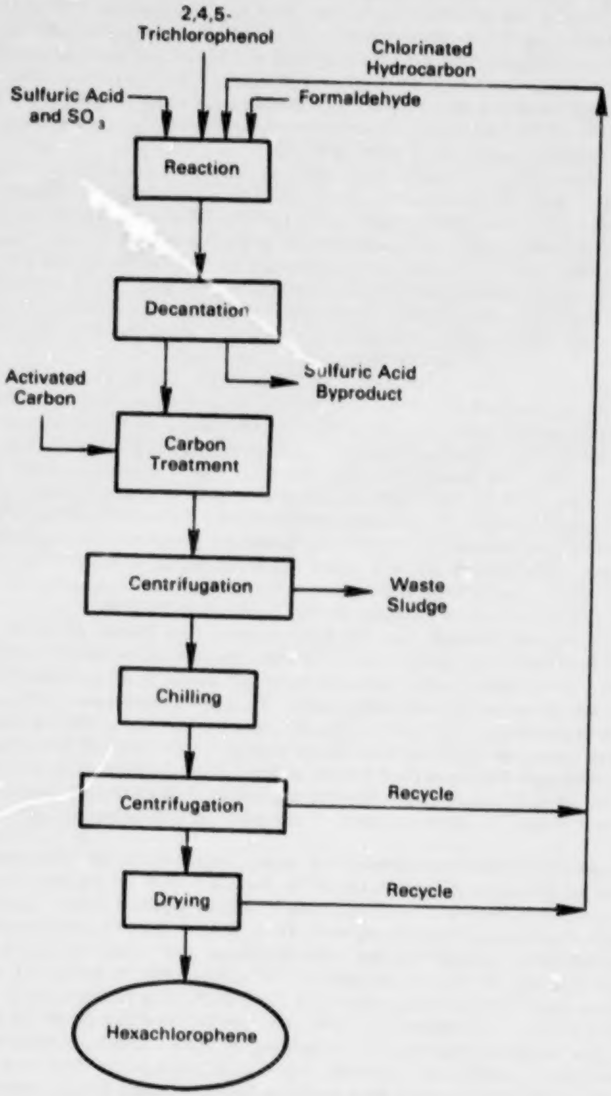
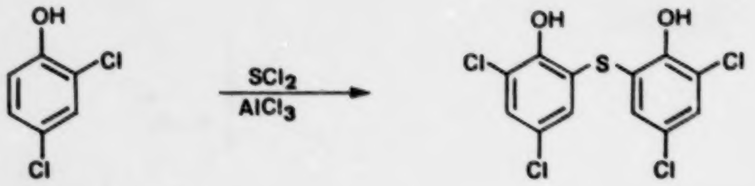


Figure 32. Flow chart for hexachlorophene manufacture.

Bithionol—

Bithionol (2,2′-thio-bis[4,6-dichlorophenol]) is an antimicrobial agent that was approved at one time for drug use by the U.S. Food and Drug Administration. This approval was withdrawn in October 1967 because the chemical was found to produce photosensitivity among users (Kimbrough 1974; Merck Index 1978). The U.S. EPA continues to approve its use as a pesticide in three animal shampoo formulations. These formulated bithionol products may no longer be actively marketed, however, because the single basic source of this chemical (Sterling Drug's Hilton-Davis Chemical Co.) apparently no longer produces it (Chem Sources 1975; Stanford Research Institute 1978).

The manufacture of bithionol is a one-step reaction between 2,4-dichlorophenol and sulfur dichloride (U.S. Patent Office 1962; U.S. Patent Office 1958b). Carbon tetrachloride is used as the solvent, and a small amount of aluminum chloride serves as the catalyst. Bithionol is formed in a reaction at about 50° C; batch time is about 2 hours. The chemical reaction is shown below.



BITHIONOL

Two methods of product recovery are outlined in one process patent (U.S. Patent Office 1958b). In one method, water is added and impure bithionol precipitates. To form a crude product, it is necessary only to filter the solids from the mixture and wash them several times in water and cold carbon tetrachloride. They are then dried and packaged.

Alternatively, to recover a purified product, water is added and the mixture is distilled to remove the carbon tetrachloride for recycle. Bithionol collects as an organic sediment, which is separated from the water solution by decantation, washed with water and sodium bicarbonate, vacuum-dried, redissolved in hot chlorobenzene, filtered, chilled to precipitate bithionol, and again filtered.

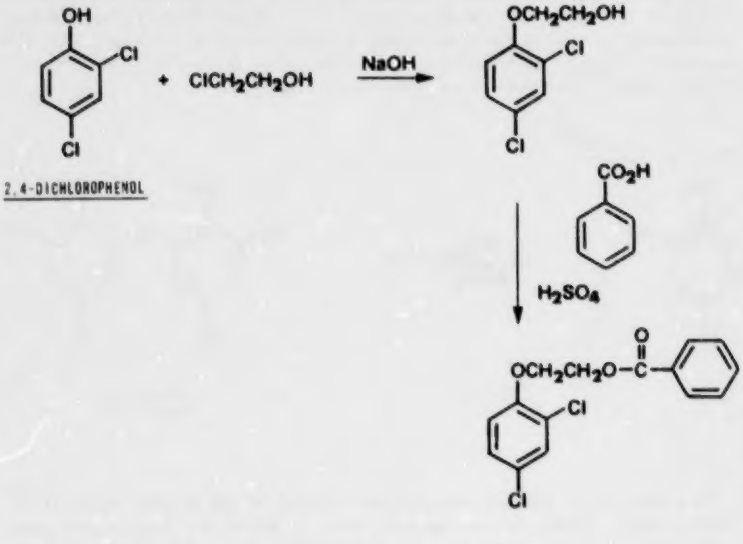
A separate patent outlines a procedure for forming metallic salts of bithionol, which are compounds that permanently impregnate cotton fabrics with disinfectant properties (U.S. Patent Office 1962). The process uses sodium hydroxide and various metallic salts in room-temperature reactions, with water as the solvent.

This manufacturing operation apparently provides no potential for production of dioxins by the known process of dioxin formation. In the manufacture of crude bithionol, there is no opportunity to reject any dioxins that may be present in the 2,4-dichlorophenol raw material. They would be carried through into the final product.

If bithionol is purified by the process outlined above, one filtration operation would remove compounds that are insoluble in hot chlorobenzene. Some dioxins, however, are slightly soluble in this solvent and thus might persist even in purified bithionol or its salts.

Sesin—

Sesin is an ester based on 2,4-dichlorophenol. The manufacture is similar to that of erbon, a 2,4,5-TCP-based herbicide described earlier. Although details of the first process step have not been reported, general organic chemical references indicate that sesin manufacture probably begins by a reaction between 2,4-dichlorophenol and ethylene chlorohydrin, as shown in the reaction sequence that follows (March 1968). Water is the most likely solvent, made strongly alkaline with sodium hydroxide, and the intermediate probably precipitates on addition of acid and is filtered from solution and dried.



SESIN

A process patent discloses that the second reaction step is a combination of the intermediate with benzoic acid (U.S. Patent Office 1956d). Xylene is the solvent, and a small amount of sulfuric acid is used to remove the water formed in the reaction.

The resulting reaction mixture is neutralized with sodium carbonate and is then fractionally distilled under vacuum to recover the xylene for recycle and possibly to separate the product from any impurities.

The first step of the reaction is the one that could possibly form dioxins. Both the raw material and the resulting intermediate contain a chlorine atom ortho to a ring-connected oxygen atom, and the mixture is heated with sodium hydroxide. High temperature is not present, however. Since water is probably the solvent, this simple reaction would not ordinarily require application of pressure. Dioxin formation could occur at the surface of steam coils if high-pressure steam is used for distillation.

Apparently no operation other than the final distillation would remove any dioxin contamination from this material. Even this distillation may not isolate dioxins into a waste stream. Most dioxins either formed by the process or present in the raw material would probably be collected with the final product.

Triclofenol Piperazine—

A pharmaceutical compound can be made from commercial 2,4,5-trichlorophenol for use as an anthelmintic (deworming medication) (U.S. Patent Office 1961a; Short and Elslager 1962). The research and animal tests of this drug were conducted prior to 1962 with unpurified commercial-grade 2,4,5-TCP. The drug was made by dissolving the chlorophenol in warm benzene and adding a measured quantity of piperazine. The resulting solution was filtered to remove insoluble matter, diluted with petroleum ether, and chilled. Crystals of the drug precipitated and were filtered from the mixture, washed with petroleum ether, dried, and packaged in gelatin capsules.

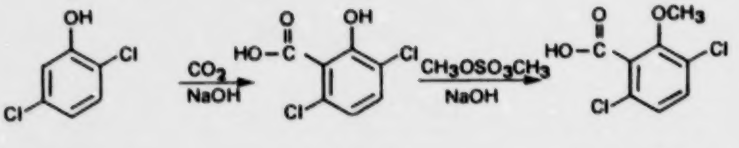
If this drug is being manufactured, the volumes are very low because it is not listed in most pharmaceutical trade references. Manufacture would probably be by the same process used in the laboratory, probably in very small batches, and with equipment not much larger than standard laboratory apparatus.

Any dioxins present in the TCP raw material are probably discharged in plant wastes rather than being concentrated into the pharmaceutical. Most of the dioxin probably is filtered from the benzene solution as part of the insoluble matter. Since some dioxins are slightly soluble in both benzene and petroleum ether, a portion might remain in solution and be transferred to solvent recovery distillation columns. The remaining dioxin would be discarded as part of an anhydrous tar from the base of these columns. The pharmaceutical industry usually incinerates both solid organic residues and solvent recovery tars.

Dicamba—

The herbicide dicamba is a derivative of salicylic acid known chemically as 3,6-dichloro-2-methoxybenzoic acid. In 1972, analysis of eight samples indicated no tetra-, hexa-, or hepta-CDD's at a detection level of 0.5 ppm (Woolson, Thomas, and Ensor 1972). The presence of DCDD's is theoretically possible, however (see Figure 23, p. 70).

Dicamba is made by acylation of 3,6-dichlorosalicylic acid, which in turn is made from 2,5-dichlorophenol. The chemical reactions are shown below.



2,5-DICHLOROPHENOL

DICAMBA

The first step is known as the Kolbe-Schmitt reaction and is also used to make unsubstituted salicylic acid from unsubstituted phenol in addition to haloginated derivatives (U.S. Patent Office 1955a). Operating temperature is probably below 200° C, and operating pressure is probably greater than 8 atmospheres. The chlorinated salicylic acid is mixed into water and sodium hydroxide and treated with dimethyl sulfate (U.S. Patent Office 1967a). The reaction is conducted initially with refrigeration to retard the otherwise violent reaction; the mixture is then heated for a few hours at reflux temperature (slightly above 100° C).

On completion of the reaction, the mixture is acidified with hydrochloric acid. Dicamba precipitates and is filtered from the mixture, rinsed with water, and dried. Recrystallization from an organic solvent such as ether is possible, but probably is not conducted in commercial practice.

Except for high temperature, all conditions necessary for formation of chlorinated dioxins are present. It is likely that at high temperature dicamba would lose carbon dioxide in a reversal of the initial manufacturing reaction, and any dioxins formed would not contain carboxyl groups.

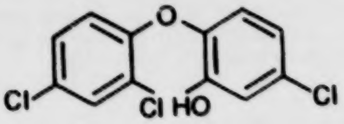
Dicamba is reported to be made by Velsicol Chemical Corporation in Beaumont, Texas, under the trade name Banvel (Stanford Research Institute 1978). It is commercially available in many formulated pesticide products.

Other Chlorophenol Derivatives—

Compounds other than the products listed above are also potential dioxin sources, but are made and used in smaller volumes.

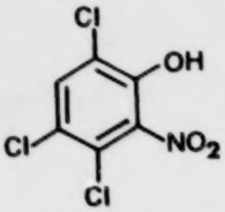
A compound with the trade name of Irgasan B5200 is used as a bacteriostat and a preservative. Often described by the generic abbreviation TCS, it is an acid amide derivative of a chlorinated salicylic acid, made by first reacting 2,4-dichlorophenol with sodium hydroxide and carbon dioxide at high pressure, then reacting the resulting intermediate with 3,4-dichloroaniline (U.S. Patent Office 1955a).

The germicide Irgasan DP-300 is a predioxin that was once sold in this country by Ciba-Geigy Corporation. As outlined in Section 2, it was used in some of the research of chlorinated dioxin chemistry, and dioxins were formed readily on heating of this compound. Its chemical formula is as follows:



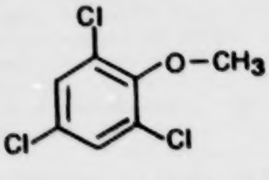
This compound is a derivative of 2,4-dichlorophenol, although the process of manufacture has not been reported.

The formulation called Dowlap was once used in the Great Lakes to control the sea lamprey, an eel-like fish. The active ingredient of the formulation was 3,4,6-trichloro-2-nitrophenol, whose chemical formula is as follows:



This compound was made by direct nitration of 2,4,5-trichlorophenol using concentrated nitric acid in a solvent of glacial acetic acid (Merck Index 1978).

A dye assistant chemical for use with polyester fibers was once made with the trade name Tyrene (Merck Index 1978). Its chemical name is 2,4,6-trichloroanisole or 2,4,6-trichloromethoxybenzene, with a structural formula as follows:



It was probably made by acylation of 2,4,6-trichlorophenol with dimethyl sulfate.

Dioxins in Chlorophenol Production Wastes

Although the dioxin content of many products containing chlorophenols or their derivatives has been reported in the literature, little information is available on dioxins in the industrial wastes created by chlorophenol manufacture. One unpublished report (U.S. Environmental Protection Agency 1978d) describes analysis for dioxins in 20 samples of liquid wastes from plants manufacturing trichlorophenol, pentachlorophenol, and hexachlorophene. The limit of detection was 0.1 ppm. No TCDD's were detected in any of the samples. Hexa-, hepta-, and octachlorodioxins were found in the pentachlorophenol wastes. The report does not indicate clearly whether any of the higher chlorodioxins were found in the hexachlorophene wastes.

Considerations of solubility and volatility suggest that large concentrations of dioxins will be found in the still bottom wastes from 2,4,5-TCP manufacture. Direct analytical evidence to this effect, though limited, is affirmative. Waste oils identified as early 1970 still residues from a former 2,4,5-TCP manufacturing plant in Verona, Missouri, have been analyzed and reported to contain ppm quantities of 2,3,7,8-TCDD (Johnson 1971; Commoner and Scott 1976a). A toluene still bottom waste taken from Transvaal's plant in Jacksonville, Arkansas, has recently been found to contain 40 ppm of TCDD's (Watkins 1979; also see Section 4 of this report).

The effect of biological treatment on removal of dioxins from liquid industrial wastes is not known. In 1978, the Dow Chemical Company reported that no 2,3,7,8-TCDD could be detected in 13 of 14 grab and composite samples from the secondary and tertiary outfall of its manufacturing plant, which produces large quantities of 2,4,5-TCP, 2,4,5-T, and other chlorophenolic compounds; one sample was questionable. The reported level of detection ranged from 1 to 8 ppt. No information is given on the dioxin content of the untreated waste stream or on the treatment methods.

Apparently it has been common practice for chemical manufacturers to dispose of dioxin-contaminated wastes or other toxic chemical wastes by landfill. Either liquid or solid forms of the wastes are placed in drums and stored or buried. Dioxin wastes disposed of in this manner would be expected to be quite concentrated. Recently ppt to ppb levels of TCDD's were reported in environmental samples from two landfills in Niagara Falls, New York (Chemical Week 1979). Hooker Chemical reportedly has dumped a total of 3700 tons of 2,4,5-trichlorophenol wastes over the past 45 years in these two dumps (Hyde Park and Love Canal) and in one other disposal site on the company's Niagara Falls property. The report estimated that the wastes buried in these landfills could contain over 100 pounds of TCDD's.

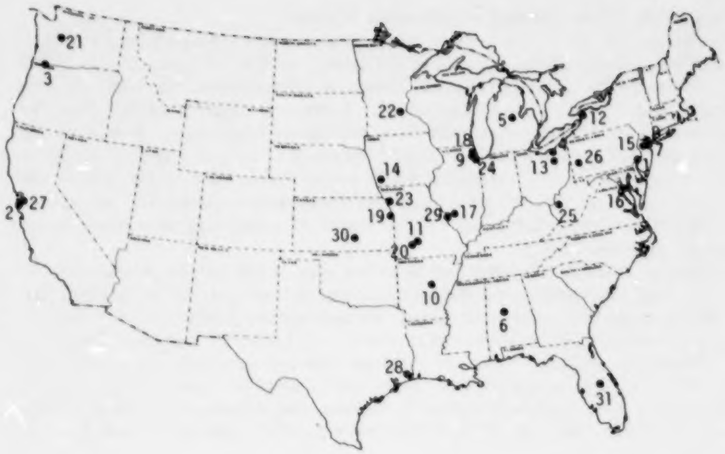
At the Transvaal pesticide plant in Jacksonville, Arkansas, more than 3000 barrels of dioxin-contaminated wastes are stored on the plant property (Fadiman 1979). The total quantity of TCDD present in the wastes has not been estimated.

No other known information describes the quantities of dioxins that might be buried elsewhere in the United States. In an effort to identify areas where landfills are most likely to contain large dioxin wastes, Figure 33 illustrates the locations where chlorophenols and their derivatives are now or were formerly produced. A list of these locations is presented in Table 19; note that this list does not include locations of the many companies that are believed only to formulate or otherwise merchandise the chlorophenols or their derivatives.

A detailed discussion of the methods used for disposal of dioxins is presented in Section 8. Additional information related to the environmental effects of dioxin disposal is presented in the subsection on Water Transport in Section 7.

HEXACHLOROBENZENE

In 1974, a technical paper reported the presence of OCDD in samples of commercial hexachlorobenzene (Villaneuva et al. 1974). Three samples were



1. Philadelphia, PA
2. San Mateo, CA
3. Portland, OR
4. Cleveland, OH
5. Midland, MI
6. Tuscaloosa, AL
7. Linden, NJ
8. Clifton, NJ
9. Naperville, IL
10. Jacksonville, AR
11. Springfield, MO
12. Niagara Falls, NY
13. Dover, OH
14. Shenandoah, IA
15. Rahway, NJ
16. Whiteford, MD
17. Sauget, IL
18. Chicago, IL
19. Kansas City, KS
20. Verona, MO
21. Tacoma, WA
22. St. Paul, MN
23. St. Joseph, MO
24. Chicago Heights, IL
25. Nitro, WV
26. Ambler, PA
27. Fremont, CA
28. Port Neches, TX
29. St. Louis, MO
30. Wichita, KS
31. Orlando, FL

Figure 33. Locations of current and former producers of chlorophenols and their derivatives.

TABLE 19. LOCATIONS OF CURRENT AND FORMER PRODUCERS OF CHLOROPHENOLS AND THEIR DERIVATIVES[a]

Producer	Location	Chemical Type
Alco Chemical Corp.	Philadelphia, PA	2,4-D
J. H. Baxter and Company	San Mateo, CA	PCP
Chempar	Portland, OR	2,4,5-T 2,4-D
Diamond Shamrock Corp.	Cleveland, OH	2,4,5-TCP 2,4,5-T 2,4-D
Dow Chemical Company	Midland, MI	2,4,5-TCP 2,4,6-TCP 2,3,4,6-Tetrachlorophenol 2,4-D 2,4,5-T Silvex Ronnel Erbon DMPA
Fallek-Lankro Corp.	Tuscaloosa, AL	2,4-D
GAF	Linden, NJ	2,4-D
Givaudan Corporation, Chemicals Division	Clifton, NJ	Hexachlorophene
Guth Corp.	Naperville, IL	2,4-D
Hercules, Inc.[b]	Jacksonville, AR	2,4-D Silvex 2,4,5-TCP
Hoffman-Taft, Inc.	Springfield, MO	2,4,5-T
Hooker Chemical Corp. Occidental Petroleum Corp., subsidiary	Niagara Falls, NY	2,4,5-TCP
ICC Industries, Inc., Dover Chemical Corp., subsidiary	Dover, OH	PCP
Imperial, Inc.	Shenandoah, IA	2,4-D
Merck and Co., Inc.	Rahway, NJ	2,4,5-TCP
Miller Chemicals, Alco Steel subsidiary	Whiteford, MD	2,4-D

(continued)

TABLE 19. (continued)

Producer	Location	Chemical Type
Monsanto Company Monsanto Industrial Chemicals Company	Sauget, IL	PCP 2,4,5-T 2,4-D
Nalco Chemical Co.	Chicago, IL	PCP 2,4,5-TCP
North American Phillips Corp., Thompson-Hayward Chemical Co., subsidiary	Kansas City, KS	2,4-D 2,4,5-T Silvex
North Eastern Pharmaceuticals	Verona, MO	2,4,5-TCP
PBI-Gordon Corporation[c]	Kansas City, KS	2,4-D 2,4,5-T
Private Brands, Inc.[c]	Kansas City, KS	2,4-D 2,4,5-T
Reichhold Chemicals, Inc.	Tacoma, WA	PCP
Rhodia, Inc. Agricultural Division	Portland, OR St. Paul, MN St. Joseph, MO	2,4-D 2,4-DB
Riverdale Chemical Co.	Chicago Heights, IL	2,4-D 2,4,5-T Silvex
Roberts Chemicals, Inc.	Nitro, WV	2,4,6-TCP
Rorer-Amchem Amchem Products, Inc., Division[d]	Ambler, PA Fremont, CA St. Joseph, MO	2,4,5-T 2,4-D
Sanford Chemicals	Port Neches, TX	2,3,4,6-Tetrachlorophenol PCP
Thompson Chemicals	St. Louis, MO	2,4,5-T 2,4-D
Union Carbide Corp. Agricultural Products Division Amchem Products, Inc., subsidiary[d]	Ambler, PA Fremont, CA St. Joseph, MO	2,4-D 2,4,5-T
Vertac, Inc. Transvaal, Inc., subsidiary[b]	Jacksonville, AR	2,4,5-TCP 2,4-D 2,4,5-T Silvex

(continued)

TABLE 19. (continued)

Producer	Location	Chemical Type
Vulcan Materials Co. Chemicals Division	Wichita, KS	PCP
Woodbury Comutrix subsidiary	Orlando, FL	2,4-D

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a—Sources: Stanford Research Institute Directory of Chemical Producers, United States 1976, 1977, 1978, and 1979. U.S. Tariff Commission. Synthetic Organic Chemicals, United States Production and Sales 1968. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales 1974, 1976, 1977, and 1978.

b—Hercules, Inc., was a former owner of the Jacksonville, AR, facility now owned by Vertac, Inc.

c—Private Brands, Inc., is believed to be a former owner of the Kansas City, KS, facility now owned by PBI-Gordon Corp.

d—Former Rorer-Amchem facilities in Ambler, PA; Fremont, CA; and St. Joseph, MO, are now owned by Union Carbide Corp.

analyzed, two of which contained OCDD in concentrations of 0.05 and 211.9 ppm. All three contained octachlorodibenzofuran (OCDF) in concentrations of 0.34, 2.33, and 58.3 ppm. One sample contained a trace amount of heptachlorodibenzofuran. It was established that the principal impurity in these samples was pentachlorobenzene in amounts ranging from 0.02 percent to 8.1 percent. When the samples were examined qualitatively, 11 other impurities having polychlorinated ring-type structures were identified:

Octachlorobiphenyl
Decachlorobiphenyl
1-Pentachlorophenyl-1,2,3-dichloroethylene
Decachlorobiphenyl
Octachlorobiphenylene
Octachloro-1,1-bicyclopentadienylidene
Hexachlorocyclopentadiene
Nonachlorobiphenyl
Decachlorobiphenyl
Pentachloroiodobenzene
Heptachloropilium

It is significant that this list includes no phenolic compounds and no predioxins or isopredioxins. In fact, the only compounds in these samples that contain oxygen are dioxins and dibenzofurans.

Uses

Hexachlorobenzene is a registered pesticide formerly used to control a fungus infection of wheat. It is also a waste byproduct from manufacturing plants that produce chlorinated hydrocarbon solvents and pesticides (Villaneuva 1974; U.S. Environmental Protection Agency 1978g). It can be used as a raw material in the manufacture of pentachlorophenol, but is not so used in this country.

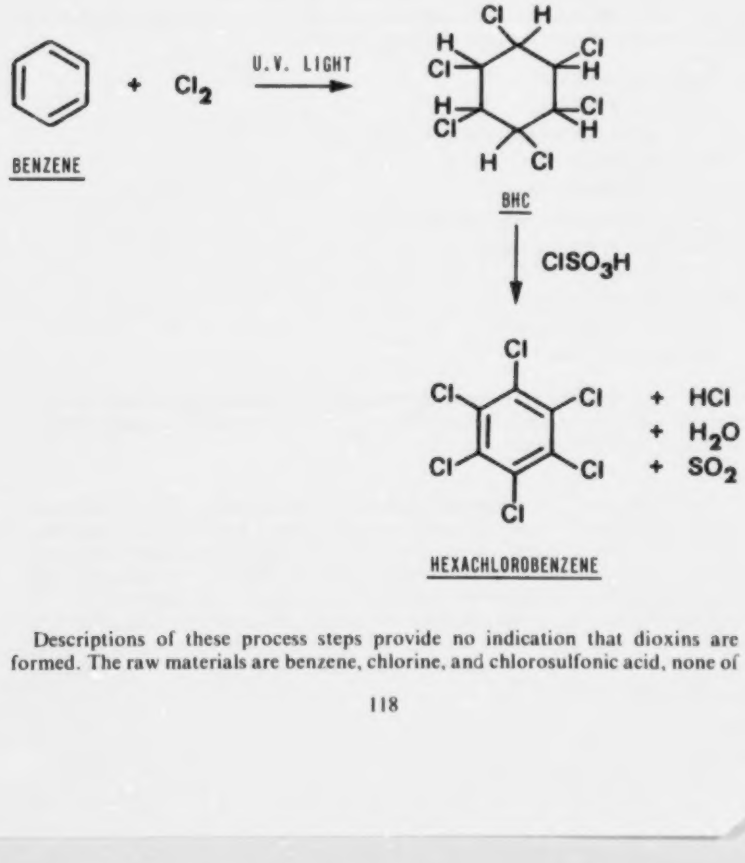
Hexachlorobenzene is not the same compound as benzene hexachloride. The empiric formula of hexachlorobenzene (HCB) is C_6Cl_6, and its structure is that of benzene in which all of the hydrogen atoms have been replaced with chlorine.

Benzene hexachloride (BHC) is the common name of hexachlorocyclohexane. Its empiric formula is $C_6H_6Cl_6$, and its structure results from direct addition of chlorine to benzene rather than from replacement of hydrogen. One stereoisomer of BHC, the gamma form, is a powerful insecticide, and its use in this country is severely restricted. It is still made, however, because BHC is an intermediate in the most common synthesis method of producing HCB.

Manufacture

In the manufacture of HCB, the first step is a photochlorination, in which chlorine gas is bubbled through benzene (Wertheim 1939; U.S. Patent Office 1955b). This occurs in a specialized reaction vessel fitted with a strong source of ultraviolet light. In a low-temperature reaction, the light catalyzes the conversion of approximately 25 percent of the benzene into a mixture of BHC isomers. This mixture is "crude" BHC, consisting of about 65 percent of the alpha isomer, 10 percent beta, 13 percent gamma, 8 percent delta, and 4 percent epsilon. It is separated by distilling off most of the excess benzene for recycle and then filtering the BHC crystals from the mixture.

All stereoisomers of BHC are equally suitable for the manufacture of HCB. The continuation of the process consists of mixing BHC with chlorosulfonic acid or sulfuryl chloride and holding the mixture at approximately 200° C for several hours (U.S. Patent Office 1957a). This step removes the hydrogen from BHC and thereby restores the unsaturated benzene ring. When the mixture is cooled, HCB precipitates and is separated by filtration, rinsed with water, dried, and packaged. The following shows the overall chemical reactions of the process.



Descriptions of these process steps provide no indication that dioxins are formed. The raw materials are benzene, chlorine, and chlorosulfonic acid, none of which are likely sources of dioxins. The only reactant that could contribute the oxygen needed to complete the dioxin ring is chlorosulfonic acid, but in this compound the oxygen is tightly bound in a linkage with sulfur.

There is, however, a supplemental process that contributes other chemicals that may lead to dioxin formation. This extra step may be conducted at some plants, or may have been conducted in earlier years. If a market exists for the sale of gamma-BHC as an insecticide, this material is extracted from the mixture of crude BHC and benzene after most of the excess benzene has been distilled off for recycle. To this concentrated solution, water is added, along with other chemicals. The objective is to form an emulsion that will entrain part of the BHC. The solution is then filtered; the emulsion passes through the filter, while the solids that were not emulsified are captured. Since gamma-BHC accumulates preferentially in the emulsion, the solids from this first filtration are used for HCB manufacture and the filtrate is treated with salt to break the emulsion and then refiltered. The second crop of solids contains up to three times as much gamma-BHC as the crude product and is dried and sold separately (U.S. Patent Office 1955b).

As indicated by the process patent, chemicals added during this supplemental step include a wide range of organic detergents and solvents, but none of those listed are phenolic or have been shown to create dioxins. Detergents of the anionic type are preferred, especially salts of sulfonated succinic esters, although any of the common surface-active agents are suitable. Supplemental solvents may not be employed, since benzene alone is said to be preferred, but other suitable solvents include dioxanes, any of the aliphatic substituted benzenes, any of the common chlorinated paraffin hydrocarbons, kerosenes, and ethyl ether. Dioxane is the one compound listed that might contribute to dioxin formation, although the reaction is not reported in published literature.

Production

Current information on the volume or production of hexachlorobenzene is uncertain. Annual production estimates range from 420,000 to 700,000 pounds. Stauffer was the only reported domestic producer in 1974; Dover Chemical Company of Niagara Falls, New York, was the only reported producer in 1977 (U.S. Environmental Protection Agency 1978g). Dioxins have not been reported in any other chlorobenzene compounds.

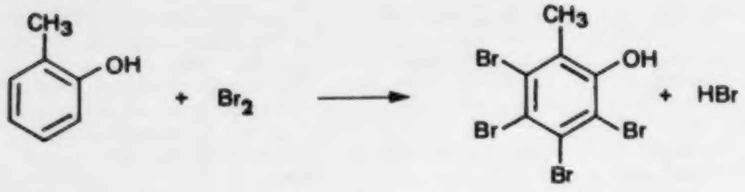
OTHER PHENOLIC COMPOUNDS WITH DIOXIN-FORMING POTENTIAL

Several compounds with a phenol nucleus that do not contain chlorine are now being manufactured or were manufactured at one time. Four such compounds or classes of compounds are examined for their dioxin-forming potential in this section. (See also Table 7, page 38)

Brominated Phenols

Three brominated phenolic compounds were once manufactured, and may still be. Because brominated dioxins have been made in laboratory experiments, they may be created during the manufacture of these compounds.

Published data describe the production method for tetra-bromo-cresol, which is made by direct bromination of *o*-cresol in a solvent of carbon tetrachloride with aluminum and iron powders as catalysts (U.S. Patent Office 1943). The following reaction is conducted at room temperature, and it requires about 24 hours to complete a batch.



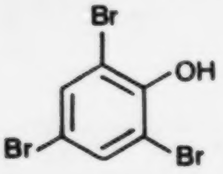
O-CRESOL

TETRABROMO-O-CRESOL

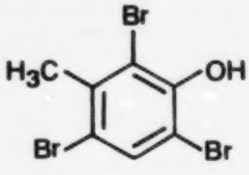
When the reaction is complete, the mixture is heated to about 80° C to drive off the carbon tetrachloride solvent and excess bromine. The residue is mixed with dilute hydrochloric acid to form a slurry, which is then filtered. The resulting solids are washed with water, dried, and packaged. Yield is about 95 percent.

It is possible to recrystallize this product to separate nonphenolic impurities by dissolving the crude product in sodium hydroxide solution, filtering out insolubles, neutralizing the mixture with hydrochloric acid, and refiltering. This step may or may not be conducted in commercial practice.

Two other brominated phenolic compounds are believed to be made by essentially the same process. Structural formulas are as follows:



2,4,6-TRIBROMOPHENOL



2,4,6-TRIBROMO-M-CRESOL

Almost all brominations of organic compounds are low-temperature processes because bromine is readily vaporized and would be driven from the reaction vessels at high temperatures. A metallic catalyst is needed to activate the diatomic liquid bromine, and a volatile solvent is usually employed to maintain all reactants in the liquid state.

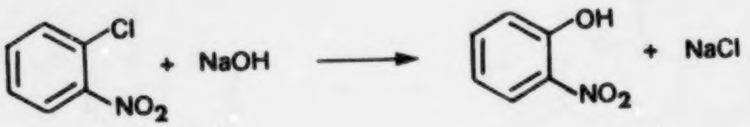
Because the temperature during manufacture of these compounds does not usually exceed 80° C except at the surface of heating coils, dioxin formation would not be expected. If dioxin contamination enters with the raw materials, brominated dioxins likely would appear in the crude product. If the product is recrystallized, the dioxins could be constituents of a waste sludge.

The literature mentions dioxins that are both brominated and methylated (see Table 5). By the known process of dioxin formation, 2,4,6-tribromo-*m*-cresol would be expected to form several dimethyltetrabromodioxins, and other cresols would also, in theory, form dimethyl dioxins.

O-Nitrophenol

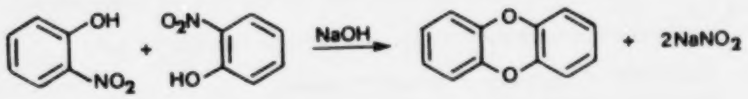
There is no direct utilization of *o*-nitrophenol as a completed chemical. It is a chemical synthesis intermediate, although it has fewer uses than *p*-nitrophenol.

The manufacture of *o*-nitrophenol is a hydrolysis of *o*-nitrochlorobenzene with sodium hydroxide in a process essentially identical to the hydrolysis method of chlorophenol production. The chemical reaction is as follows:



Although the operating conditions of this reaction are not known, conditions of temperature are probably mild. In nitrochlorobenzenes, the chlorine atom is weakly attached, especially when the substituents are in the ortho position. The chlorine atom behaves like that of an alkyl halide and is readily replaced. In contrast, the nitro group is very strongly attached and its replacement is difficult (Wertheim 1939).

Unsubstituted dioxin would be created if a further reaction did occur to remove the nitrate group by the following theoretical reaction:

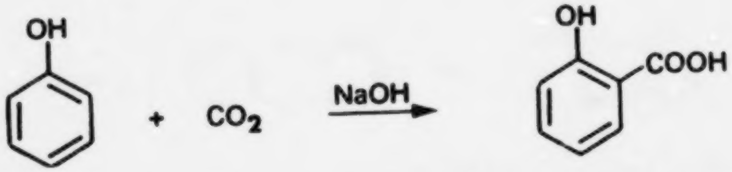


This reaction is possible, and *o*-nitrophenol may be a source of dioxin contamination.

This compound is manufactured by the Monsanto Company, Sauget, Illinois.

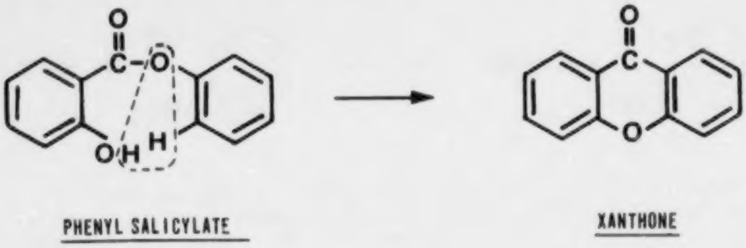
Salicylic Acid

Salicylic acid is an important chemical synthesis intermediate used to make dyes, flavoring chemicals, and pharmaceutical compounds such as aspirin. Unsubstituted dioxin may be present, but has not been reported. Salicylic acid is made by a high-pressure reaction between phenol and carbon dioxide in the presence of sodium hydroxide; this reaction is known as the Kolbe-Schmitt reaction.



Operating temperature is about 150° C. Higher temperatures are avoided to prevent a side reaction that forms *p*-hydroxybenzoic acid.

This process includes some of the conditions needed to produce unsubstituted dioxin, but not all of them. The hypothesis of possible dioxin formation is strengthened, however, by observations of products created by thermal decomposition of salicylic acid. When heated strongly, it decomposes primarily into phenol and carbon dioxide, but also into smaller amounts of phenyl salicylate, which in turn condenses to xanthone:



Since the ortho carbon is held weakly in the salicylic acid molecule, and since the triple-ring xanthone structure has been identified, the formation of dioxins may also be possible, especially if oxygen is present.

Both salicylic acid and xanthone are widely distributed in nature. Salicylic esters are responsible for some plant fragrances, and xanthone is a yellow pigment in flowers.

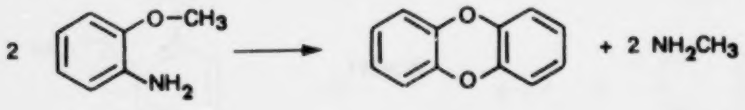
Salicylic acid is manufactured by four companies in this country:

Dow Chemical Company—Midland, Michigan
Monsanto Company—St. Louis, Missouri
Hilton-Davis Chemical Company—Cincinnati, Ohio
Tenneco Chemicals, Inc.—Garfield, New Jersey

The combined capacity of these four plants is 24 million kilograms annually.

Aminophenols

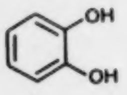
The *o*-aminophenols could conceivably form dioxins through condensation with loss of ammonia. These are not high-volume chemicals and are not known to be made with halogen substituents. A class of related compounds is used in much larger quantity; these are the derivatives of *o*-anisidine (methoxyaminobenzene), which in several forms are important dye intermediate chemicals. These might condense in appropriate environments into the dioxin structure through loss of methylamine. The environments would probably be acidic:



Although this reaction is possible, it is unlikely because the amine group is tightly bound to the benzene ring. Aminophenols or similar compounds are not likely sources of dioxin contamination.

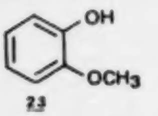
DIOXINS IN PARTICULATE AIR EMISSIONS FROM COMBUSTION SOURCES

Recent reports by chemists at the Dow Chemical Company maintain that dioxin formation is a natural consequence of combustion (Dow 1978). There are numerous naturally occurring compounds that could, during the complex process of combustion, serve as precursors of dioxins. Combustion of these compounds in the presence of chlorine-containing compounds (e.g., DDT or polyvinyl chloride) could lead to the formation of chlorinated dioxins. Examples of such naturally occurring "potential" dioxin precursors are given below.



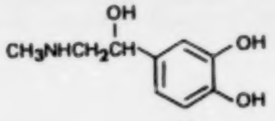
22

CATECHOL



23

GUAIACOL

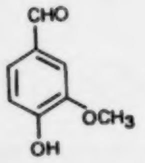


24

ADRENALINE

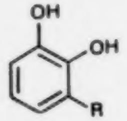
(EPINEPHRINE)

Catechol (22) occurs in nature as the product of phenol biodegradation and as a major product of tannin pyrolysis (Wertheim 1939). Guaiacol (23) occurs as the major phenolic component in several hardwood trees and is also prepared synthetically for use as an ingredient in cough syrups (Merck 1978; U.S. EPA Draft 1979). Adrenaline (24) is a naturally occurring mammalian hormone and is also prepared synthetically for use in many drug formulations (U.S. EPA Draft 1979). Other naturally occurring compounds that contain the orthohydroxy or alkoxy groups include vanillin (25), which is the flavoring ingredient in vanilla extract; urushiol (26), a mixture of compounds that are the toxic constituents of poison ivy; eugenol (27), the pungent principle of cloves; capsaicin (28) the pungent principle of various peppers; and safrole (29), the major volatile constituent of sassafras.



25

VANILLIN



26

R = $C_{15}H_{31}$

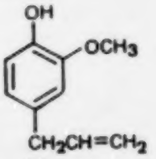
= $C_{15}H_{29}$

= $C_{15}H_{27}$

= $C_{15}H_{25}$

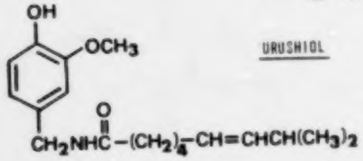
= $C_{15}H_{23}$

URUSHIOL



27

EUGENOL



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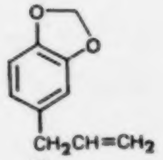
CAPSAICIN

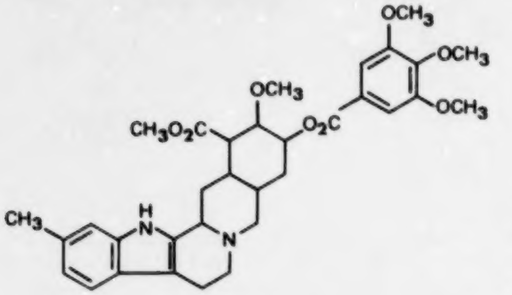


29

SAFROLE

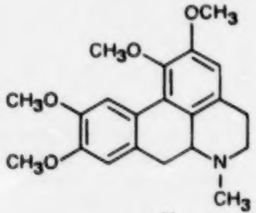
Among many plant alkaloids that include the structure are reserpine (30), glaucine (31), and colchicine (32). Other potential dioxin precursors are found in the fomecin (33) series of antibiotics, produced by a fungus, and also in one of the active ingredients of creosote.

A constituent of animal urine is 4-hydroxy-3-methoxymandelic acid (Merck Index 1978). Since the structure is so common in living organisms, it is also often used in synthetic medicinal compounds, including phenisonone, isoproterenol, estil (an anaesthetic), methocarbanol, and the high-volume drugs guaifenesin and methyldopa (U.S. Environmental Protection Agency 1979).



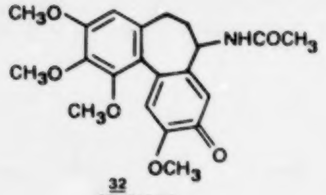
30

RESERPINE



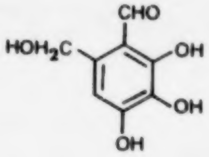
31

GLAUCINE



32

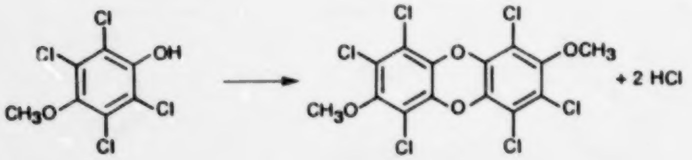
COLCHICINE



33

FOMECIN

At least one natural compound may be by itself a precursor for a chlorinated dioxin. A microorganism species creates a defensive chemical known as drosophyllin A (34), (*p*-methoxytetrachlorophenol) (Merck Index 1978). In theory it could, when heated, form a substituted hydroxy or methoxy chlorinated dioxin, one possibility of which is:



34

DROSOPHYLLIN A

Several reports describe the occurrence of dioxins in fly ash and flue gases from municipal incinerators and industrial heating facilities. In 1977, analysis of samples of fly ash from three municipal incinerators in the Netherlands showed 17 different dioxins (5 TCDD's, 5 penta-CDD's, 4 hexa-CDD's, 2 hepta-CDD's, and OCDD) (Olie, Vermeulen, and Hutzinger 1977). Although the specific number of isomers was not stated, the same dioxins were found in flue gas from one of the incinerators. In addition, large amounts of di-, tri-, and tetrachlorophenols were found in flue gases, and high levels of chlorobenzenes, especially hexachlorobenzene, were detected in all fly ash samples.

Another team of investigators reported finding the same dioxins in Switzerland (Buser and Bosshardt 1978). This study quantitatively determined that the total amount of polychlorinated dibenzo-*p*-dioxins in the fly ash from a Swiss municipal incinerator and industrial heating facility were 0.2 ppm and 0.6 ppm, respectively. High-resolution gas chromatography was then used to identify 33 specific dioxin isomers found in the fly ash samples. The dioxin isomers known to be most toxic, which are 2,3,7,8-TCDD, 1,2,3,7,8-penta-CDD, 1,2,3,6,7,8- and 1,2,3,7,8,9-hexa-CDD, were only minor constituents of the total dioxins found.

Later in 1978, researchers at Dow Chemical Company reported finding ppb levels of chlorinated dioxins in particulate matter from air emissions of two industrial refuse incinerators, a fossil-fueled powerhouse, and other combustion sources such as gasoline and diesel autos and trucks, two fireplaces, a charcoal grill, and cigarettes. (See Table 20.) All of these sources are believed to be located on or near the Dow facilities in Midland, Michigan. Tetra-, hexa-, hepta-, and octachlorodioxins were found. Concentrations of 2,3,7,8-TCDD were minor relative to concentrations of other dioxins. Dow concluded from the study that their Midland facility was not a measurable source of the dioxins found in fish from nearby rivers, and that, in fact, chlorinated dibenzo-*p*-dioxins may be ubiquitous in combustion processes. A preliminary data analysis by the EPA does not entirely agree with Dow's conclusions. The EPA continues to believe that Dow's Midland plant is the major and possibly the only source of the dioxins contaminating fish in nearby rivers. The EPA has asked Dow for further clarification of the company's findings and analytical methods (Merenda 1979).

In contrast to the Dow finding of 38 ppb TCDD's in powerhouse emissions, Kimble and Gross (1980) report finding no TCDD's in fly ash from a typical commercial coal-fired power plant in California; the detection limit was 1.2 ppt. Crummett of Dow Chemical Company asserts that these studies could not have found 2,3,7,8-TCDD to be present because the solvents used for the extraction techniques in preparation for the analytical analysis were not appropriate.

In 1980 Wright State University chemists analyzed emissions from a U.S. municipal incinerator for chlorodioxins (Tiernan and Taylor 1980). TCDD's were detected in all seven samples. Isomer-specific analyses indicate that 2,3,7,8-TCDD is a minor product, and evidence was obtained for the presence of 1,3,6,8-, 1,3,7,9-, 1,3,7,8-, 1,3,6,7-, and at least six other TCDD isomers.

The formation of dioxins from the thermal decomposition of chlorophenols and their salts (chlorophenates) is well documented. In 1971, Milne reported finding no evidence of formation of lower chlorinated dioxins from the thermal decomposition of dichlorophenols; all six dichlorophenol isomers were studied. However, Aniline (1973) found that pyrolysis of 2,3,4,6-tetrachlorophenate produced two hexa-CDD isomers. Later, Stehl et al. (1973) found that burning paper treated with sodium pentachlorophenate produced OCDD, but burning either wood or paper treated with pentachlorophenol did not produce the dioxin. In 1975, a series of pyrolysis experiments was conducted with 2,3,4-, 2,3,5-, 2,4,5- and 2,3,6-tri, 2,3,4,5-, 2,3,5,6- and 2,3,4,6-tetra, and pentachlorophenates to obtain samples of many tetra-, penta-, hexa-, and octa-CDD's for study (Buser 1975). In 1977, 2,3,7,8-TCDD was found as a combustion product of many 2,4,5-trichlorophenoxy compounds, but the amount of this dioxin was very small relative to the

TABLE 20. DIOXINS IN SELECTED SAMPLES[a]
(ppb except as noted)

	TCDD's				
Source	2,3,7,8-TCDD	Other TCDD isomers	Hexa-CDD's	Hepta-CDD's	OCDD
Soil inside plant	0.3–100	0.8–18	7–280	70–3200	490–20,500
Dust samples from Dow Research Building	0.7–2.6	0.5–2.3	9–35	140–1200	650–7500
Soil and dust from Midland and metro areas	0.03–0.04		0.09–0.4	0.3–3.9	0.4–31
Soil and dust from major metro area	0.005–0.03		0.02–0.14	0.10–3.3	0.35–22
Soil and dust from urban area	none	none	0.03–1.2	0.035–1.6	0.05–2.0
Soil and dust from rural area	none	none	none	0.02–0.05	0.10–0.35
Dow stationary tar incinerator particulates	none	none	1–20	27–160	190–440
Dow rotary kiln incinerator with supplementary fuel	none	none	1.4–5.0	4–110	9–950

(continued)

TABLE 20. (continued)

Source	TCDD's 2,3,7,8-TCDD	 Other TCDD isomers	Hexa-CDD's	Hepta-CDD's	OCDD
Dow rotary kiln incinerator without supplementary fuel	110–8200	1800–12,000	1300–65,000	2000–510,000	3000–810,000
Dow powerhouse fired with fuel oil/coal	none	38	2	4	24
Automobiles					
catalytic – carbon	none	0.1	0.5–2.0	2–14	8–72
catalytic – rust	0.4	4.0	0.7	3	28
noncatalytic	none	4.0	none	3	10–16
diesel trucks	3.0	20.0	4–37	35–110	190–280
Fireplaces (scrapings)	0.1	0.27	0.23–3.4	0.67–16	0.89–25
Cigarettes (tars)	none	none	4.2–8.0	8.5–9.0	18–50
Charcoal-grilled steaks	none	none	none	3–7	5–29
Residential electrostatic precipitator	0.6	0.40	34	430	1300
Particulates from rotary kiln scrubber water with supplemental fuel	46		200	970	1200
without supplemental fuel	2500		3400	26,000	42,000

(continued)

TABLE 20. (continued)

Source	TCDD's		Hexa-CDD's	Hepta-CDD's	OCDD
	2,3,7,8-TCDD	Other TCDD isomers			
Filtered scrubber water	0.0028		0.005	0.024	0.026
Cooling tower residues	1.6–6.0		10	12–25	56–119
Sewer waters before treatment (concentration – ppt)	1–4		N.A.[b]	N.A.[b]	3-1500

a—Source: Dow Chemical Company 1978.
b—N.A. = not applicable.

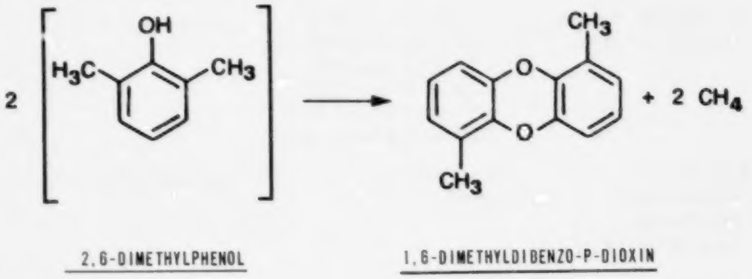
amount of the 2,4,5-trichlorophenoxy compound that was burned (Stehl and Lamparski 1977). Results of the study showed that only 1.2×10^{-5} to 5×10^{-5} percent by weight of the 2,4,5-trichlorophenoxy species was converted to 2,3,7,8-TCDD by combustion.

The origin of the dioxins in airborne particulates from combustion is not yet clarified. Rappe et al. (1978) suggest that polychlorinated dibenzo-*p*-dioxins can be formed during combustion by dimerization of chlorophenates, by dechlorination of more chlorinated polychlorinated dibenzo-*p*-dioxins, and by cyclization of predioxins. Dow Chemical Company (1978) suggests that because of the complex nature of the materials being burned and the complex chemistries of fire, the formation of chlorinated dioxins occurs in all combustion processes, i.e., that the formation is not necessarily limited to combustion in the presence of chlorophenates or chlorophenols. The presence of biosynthesized compounds with characteristics of dioxin precursors may give some credence to this contention.

An alternative explanation for the observed presence of dioxins in the fly ash of refuse incinerators is that the dioxins enter intact as contaminants of the wastes being burned. For example, silvex-treated grass clippings, sawdust or other wastes from PCP-treated wood (landscape timber, railroad ties), and "empty" PCP, silvex, or other pesticide containers from home or industrial use might be direct sources of the dioxins detected in municipal incinerator fly ash. If this were the case, seasonal variations in fly ash dioxin content would be expected, with larger amounts in spring and summer.

DIOXINS IN PLASTIC

In 1965, it was reported that dioxin is an impurity in the preparation of polyphenylene ethers (Cox, Wright, and Wright 1965). No reports further substantiating this finding are known. "PPO"is a trademark of General Electric Company for a polyphenylene thermoplastic derived from 2,6-dimethylphenol (Hawley 1971). The dioxin configuration one would expect from condensation of the dimethylphenol is as follows:



Because PPO is highly resistant to acids, bases, detergents, and hydrolysis, it may be used in hospital and laboratory equipment, and in pump housings, impellers, pipes, valves, and fittings in the chemical and food industries.

DIOXINS PRODUCED FOR RESEARCH PURPOSES

Many investigators have reported the sources of purified dioxin standards used in their studies. Some of these dioxin sources and the names of the dioxins provided are listed in Table 21.

In addition to these, Dow Chemical Company has recently published methods for preparing all of the TCDD isomers (Nestrick, Lamparski, and Stehl 1979).

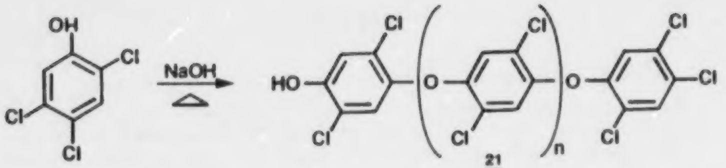
TABLE 21. SOURCES OF PURIFIED DIOXIN SAMPLES FOR RESEARCH

Source	Dioxin provided	Reference
Givaudan Ltd. Dubendorf, Switzerland	2-mono-CDD 2,3-di-CDD 2,7-di-CDD 2,8-di-CDD 1,2,4-tri-CDD 1,3,7-tri-CDD 2,3,7-tri-CDD	Buser (1978)
Dr. K. Anderson University of Umea, Sweden	1,2,3,4-tetra-CDD	Buser (1978)
Dr. C. A. Nilsson University of Umea, Sweden	1,2,3,8-tetra-CDD 1,2,3,7-tetra-CDD	Buser (1978)
Stickstoffwerke Linz, Austria	2,3,7,8-tetra-CDD	Buser (1978)
Dr. David Firestone Food and Drug Administration Washington, DC, U.S.A.	1,2,3,7,8-penta-CDD 1,2,4,7,8-penta-CDD 1,2,3,6,7,8-hexa-CDD 1,2,3,7,8,9-hexa-CDD	Buser (1978)
Dow Chemical Company Midland, MI, U.S.A.	Unspecified dioxin standards	Villanueva (1973)
ITT Research Institute Chicago, IL, U.S.A.	1,2,4,6,7,9-hexa-CDD 1,2,3,6,7,9-hexa-CDD 1,2,3,6,7,8-hexa-CDD 1,2,3,7,8,9-hexa-CDD 1,2,3,4,6,7,9-hepta-CDD 1,2,3,4,6,7,8-hepta-CDD	Firestone (1977)
A. E. Pohland Food and Drug Administration Washington, DC, U.S.A.	2,3,7,8-TCDD OCDD	Firestone (1977)
A. Poland McArdle Laboratory for Cancer Research University of Wisconsin Madison, WI, U.S.A.	^{14}C-TCDD	O'Keefe et al. (1978)
Dow Chemical Company Midland, MI, U.S.A.	hexa-CDD hepta-CDD octa-CDD	C. D. Pfeiffer (1978)

SUMMARY

In summary, dioxins can enter the environment in a variety of ways:

1. As contaminants in commercial chemical products whose normal processing conditions generate the dioxins as byproducts. Previous subsections detail the mechanisms by which this can occur in some of these commercial chemicals.
2. As contaminants in chemical processing under improperly controlled reaction conditions (Rappe 1978). Thus, dioxins would be present in the wastes from "bad batches." Chemical manufacture that might lead to dioxin presence under such circumstances is also reviewed above.
3. As products of intentional dioxin preparations in the laboratory. Although the quantities involved from such sources probably would not be large, the concentrations would be high. Therefore any failure to practice proper disposal could be serious because of the high toxicity and concentration potential. Reported laboratory dioxin preparations are noted in Section 2.
4. As deliberate or unintentional products of reactions carried out by uninformed or irresponsible persons. The hazards in such cases would be enhanced because the dioxins formed would likely be subject to improper use or disposal.
5. As products of combustion of general municipal, commercial, and industrial wastes. Such wastes are likely to contain materials required for dioxin formation. The chlorine content of municipal waste is relatively high because of the widespread use of polyvinyl chloride and other chlorinated polymers.
6. As combustion products and residues from burning vegetation that has been sprayed with chlorinated herbicides (and other pesticides). This potential source is of two-fold interest. First, chemicals such as 2,4,5-T, 2,4-D, and others noted in this section might be degraded to dioxins under relatively mild combustion conditions (Buu-Hoi 1971). Second, formation of dioxins might occur under combustion conditions, even from chemicals not directly related to dioxins, such as many insecticides (DDT, aldrin, dieldrin, etc.).
7. As incidental products of fires in facilities such as chemical and pesticide warehouses, farm buildings in which pesticides are stored, and facilities for storage of chemically treated wood products such as lumber or poles (Buu-Hoi 1971).
8. As waste disposal byproducts of materials such as polychlorinated biphenyls (PCB's). These materials have been used extensively in electrical transformers, as heat transfer media, as lubricants, and in carbonless paper.
9. As derivative wastes from pentachlorophenol (PCP) and other wood-treating agents. Agents used in the treatment of wood products are likely to remain with the wood through its use cycle. Thus they are subjected to the same extremes of exposure as the wood, including ultimately combustion, which leads to dioxin formation (Buu-Hoi 1971).
10. As an unsuspected byproduct of the treatment of aromatic compounds under oxidizing conditions at elevated temperature. Several industrial processes involve the oxidation of benzene, toluene, and naphthalene under "semicombustion" conditions. In light of such studies as that by Dow Chemical Company (Rawls 1979) on combustion sources of dioxins, the "tars" from these processes (often occurring in considerable quantities) warrant further study.
11. As byproducts of miscellaneous chemical syntheses that may not be commercially significant at this time. An example might be the detected presence of 2,3,7,8-TCDD in chlorinated polyphenylene ethers (such as 21), which can be produced from 2,4,5-trichlorophenol (Cox 1965).



These polymers are not known to be of commercial significance, but serve as a cautionary example.

12. As a result of the combustion of naturally occurring compounds.

SECTION 4

ANALYTICAL METHOD FOR DIOXINS IN INDUSTRIAL WASTES

INTRODUCTION

Most of the current technology for detection of TCDD's is based on gas chromatography and/or mass spectrometry. However, a variety of other less specific techniques have been used, including ultraviolet spectroscopy (Pohland and Yang 1972), electron spin resonance spectroscopy, and low-temperature phosphorescence emission spectroscopy (Baughman 1974). None of these methods provide both the high sensitivity and selectivity needed for analysis of most environmental samples.

A resin sorption technique using XAD-2 resin has achieved a detection limit of 1 ppt for TCDD's in water; because this technique required a large quantity of sample for extraction, however, extension to other types of samples is unlikely (Junk 1976).

Another technique uses PX21 powdered charcoal suspended on shredded polyurethane foam as the sorbant (Huckins, Stalling, and Smith 1978). The TCDD's were eluted from the charcoal column by use of a 50 percent solution of toluene in benzene and finally were detected by electron-capture gas chromatography. To enhance selectivity, an alumina column chromatography step is usually included after elution from the charcoal column. The detection limit of this method ranges from 10 to 100 ppb.

Thin-layer chromatography has also been used for the detection of TCDD's (Williams and Blanchfield 1971). Two-dimensional development with two different solvents is used to increase selectivity. The spot corresponding to 2,3,7,8-TCDD is removed from the plate, extracted with benzene, and detected by electron-capture gas chromatography. This method has achieved a detection limit in the low ppm region.

Steam distillation has also been tried (Storherr 1971), but was suitable only for levels of TCDD's in the range of 1 to 3 ppm and lacked the selectivity needed to avoid interferences.

Recently, analytical methods involving chemical ionization mass spectrometry with negative ions have been published. An early communication by Hunt and co-workers (Hunt, Harvey, and Russel 1975) reported a signal-to-noise ratio of 50 from a 2-pg direct-probe insertion sample using oxygen as the reagent gas. A sensitivity 25 times higher than the direct-probe insertion method is reported for electron impact ionization. Hass et al. compare the relative sensitivities of various chemical ionization modes, including those of positive-ion versus negative-ion modes with methane, oxygen, and mixed methane/oxygen as reagent gases (Hass 1978). Positive-ion chemical ionization affords the greater sensitivity, but does not produce ions indicative of the molecular weight.

Since 1972 the personnel of the Brehm Laboratory of Wright State University have been performing sensitive dioxin analyses under programs supported by several agencies. In these investigations Brehm Laboratory has developed and applied analytical methodology for the determination of TCDD's in many types of samples, including herbicides, industrial chemicals, soils, water, air, biological tissues and fluids (both human and other animal), and combustion products and related samples (Taylor et al. 1973; Taylor, Hughes, and Tiernan 1974a,b,c; Fee et al. 1975; Hughes et al. 1975; Taylor, Tiernan, and Hughes 1974; Tiernan 1975a,b; Tiernan, Taylor, and Hughes 1975; Taylor et al. 1975, 1976, 1977, 1979; Tiernan et al. 1979; Erk, Taylor, and Tiernan 1979; Yelton, Taylor, and Tiernan 1977; Wright State University 1976). The levels of TCDD's in these samples have ranged from high parts per million (ppm) to low parts per trillion (ppt). A significant number of samples examined have been found to contain detectable amounts of TCDD's. On the basis of these findings many investigators believe that TCDD's may already be widespread contaminants in the environment.

The analytical techniques applied by Brehm Laboratory in these earlier dioxin programs have varied widely in terms of the complexity of equipment, sample preparation, and the overall sensitivity and specificity of the procedures. It is now apparent that a single basic technique, amenable to minor modifications, would be desirable for the purpose of characterizing various types of chemical samples, provided that such a technique could satisfy all the specified criteria for sensitivity, specificity, and other analytical factors.

Sensitivity in the ppt range is required because of the potent toxicity of 2,3,7,8-TCDD. The current detection capability is approaching 1 ppt in at least some sample matrices and must be developed in others, particularly chemical process wastes and sludges. Accuracy is also important in these determinations, owing to current and potential regulatory actions that hinge on the analytical data.

In 1978 the Brehm Laboratory, in a subcontractual effort with Battelle Columbus Laboratories, supported through a prime contract between Battelle and the U.S. EPA, undertook development of new analytical techniques for use in quantitating ppt levels of TCDD's in various chemical wastes. The goal in this work was to develop a unified analytical approach to the handling of a variety of chemical waste sample types and matrices.

The U.S. EPA supplied 17 test samples representing various types of chemical wastes or residues generated during the manufacture of chlorophenols and related chemicals. These samples were expected to contain TCDD's and were used in methods development by the Brehm Laboratory analysts. Presented in this section are the final results of this work. This section includes a background discussion of various analytical approaches to the detection of TCDD's, the newly developed and validated analytical method, a description of the procedures used in development of the method, and the analytical data obtained in applying the method to various industrial samples.

BASIC PRINCIPLES OF GAS CHROMATOGRAPHY, MASS SPECTROMETRY, AND COMBINED SYSTEMS

Gas Chromatography (GC)

Gas chromatography is a special form of chromatography that is used to separate the components of chemical mixtures. Several excellent references describe the technique in detail (Dal Nogare and Juvet 1962; Littlewood 1970; Jones 1970; Ambrose 1971). In gas chromatography the mobile phase is a gas and the stationary phase is either a liquid or a solid, hence the terms gas-liquid chromatography and gas-solid chromatography. Gas-liquid chromatography entails the use of a separation device, which is a column containing the liquid phase (typically a high-boiling organic silicone polymer) distributed on a highly inert solid support. Figure 34 depicts a typical gas chromatograph.

The column is maintained in an oven, in which the temperature can be controlled precisely; through the column is passed an inert, high-purity gas (e.g., helium), called the carrier gas. The carrier gas is the mobile phase and the organic silicone polymer is the liquid phase. Typically, the samples are introduced into the column

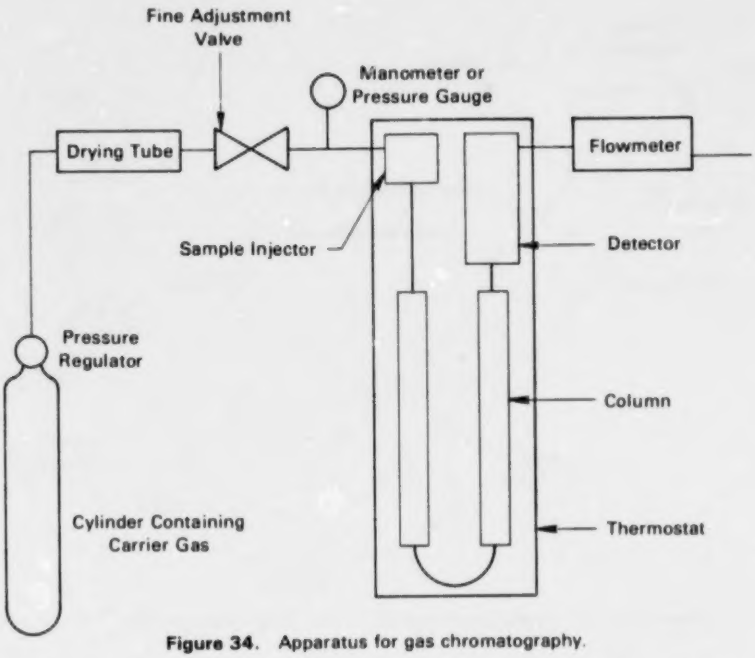


Figure 34. Apparatus for gas chromatography.

in 0.1 to 10 μl amounts with a microsyringe through an injection port, which is a heated (100° to 250° C) inlet system equipped with a silicone septum. The sample is vaporized immediately upon injection, and the inert carrier gas passing through the injection port sweeps the volatilized, injected sample out of the injection port and into the gas chromatographic column. The volatilized constituents of the sample migrate through the column at varying rates because of variations in the physical and chemical properties of each component, such as boiling point, absorptivity, and solubility. The components are thus separated and emerge (elute) from the column at different times. In some samples the components are highly similar and are not effectively separated or may necessitate the use of extraordinary chromatographic procedures. More commonly, however, the components of a chemical mixture can readily be separated by fairly simple gas chromatographic techniques.

As each separated component elutes from the gas chromatographic column, it is detected by one or more of several types of detectors. Among the widely used detectors are flame ionization, thermal conductivity, and electron capture detectors. Other, more specific, types of detectors are also used in conjunction with gas chromatography; in particular, the mass spectrometer has been used extensively. A discussion of the principles of mass spectrometry follows.

Mass Spectrometry (MS)

Mass spectrometry is described in detail in several references (Beynon 1960; McLafferty (ed.) 1963; Kiser 1965; Roboz 1968; McFadden 1973). Figure 35 is a schematic diagram of a typical mass spectrometer; the principal components of such a system are (1) an inlet system, (2) an ion source, (3) an accelerating system, (4) an analyzer system, (5) a detector, and (6) a data acquisition system. The functions of these components are described briefly.

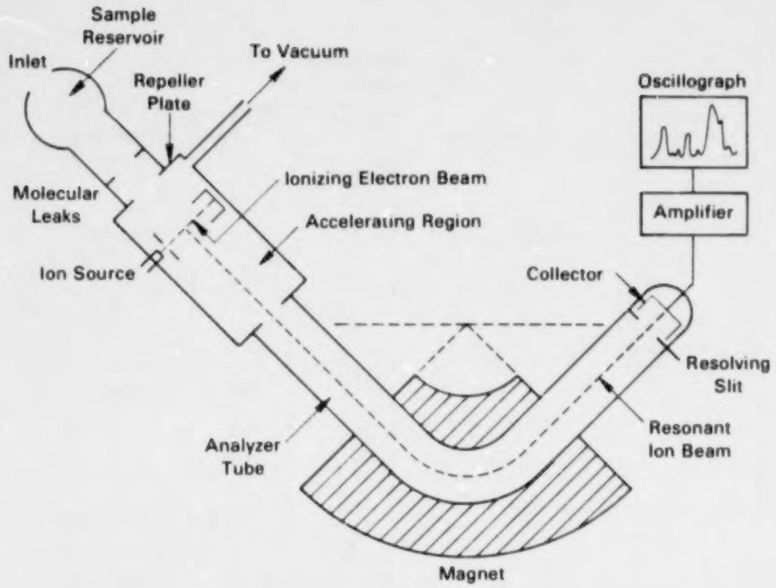


Figure 35. Schematic diagram of a Nier 60° sector mass spectrometer.

The inlet system is the means of introducing the sample into the ion source of the mass spectrometer. Inlet devices in common use include heated direct insertion probes and heated gas inlet systems (batch inlets), which are coupled to the mass spectrometer through a restricted fixed or variable orifice, often called a "leak." In recent years the gas chromatograph has been used often to introduce the sample and is coupled to the mass spectrometer—hence the term "coupled GC-MS."

Because the ion source, the accelerating lens system, the mass analyzer, and the detector of the mass spectrometer are all maintained under vacuum by a pumping system, the inlet system must admit the sample (and the carrier gas of a gas chromatograph) into the spectrometer at such a rate that the pumping system maintains the specified internal operating pressure of the instrument.

The ion source (shown schematically in Figure 36) is typically maintained at pressures of 10^{-3} mm and lower (10^{-6} mm) and at temperatures of 100° to 250° C. The source is the region in which ions are generated from the volatile sample molecules admitted through the inlet system. The ionization of molecules in the gas phase is effected by bombarding them with electrons emitted from a hot metal wire or ribbon (the filament) and drawn through a set of slits for collection at an anode or electron trap. The energy of the electrons is controlled by the potential difference between the filament and the trap. As these energetic electrons either strike or pass close to the sample molecules, ionization occurs, producing a molecular ion that usually is fragmented further to yield other ions of smaller mass. The ion source produces both positively charged and negatively charged ions, and many mass spectrometers in use today are designed to detect both types.

The ions produced are electrically forced out of the ion source and into the accelerating lens system, which generally imparts several kilovolts of energy to the ions, which then enter the mass analyzer section.

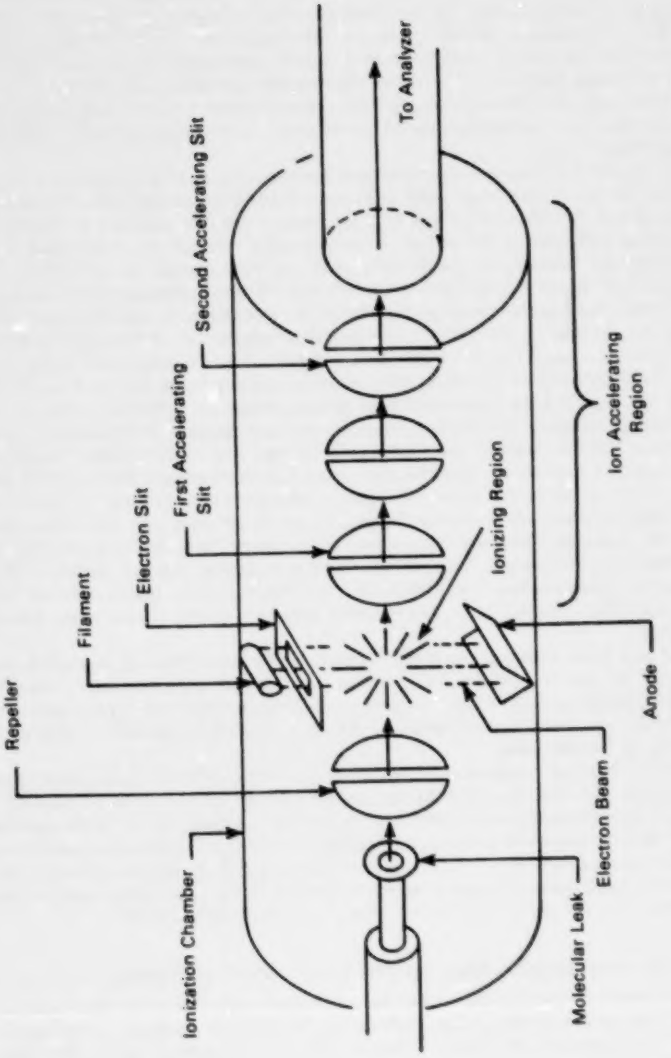


Figure 36. Electron-impact ion source and ion accelerating system.
Source: Merritt and Dean 1974.

The purpose of the mass spectrometer analyzer is to separate the ions according to their mass:charge ratios. Various types of analyzer systems are in use today, and the type of analyzer usually provides the descriptive name for each mass spectrometer system. Thus there are, for example, quadrupole mass spectrometers, single-focusing magnetic deflection mass spectrometers, time-of-flight mass spectrometers, and double-focusing mass spectrometers. Each of these systems is characterized by a distinct mode of ion separation, and each provides different capabilities.

The ability of a mass spectrometer to effect a separation of adjacent mass peaks (that is, to resolve these peaks) depends upon the analyzer. Resolution is defined by the equation, $R = M/\Delta M$, where M is the mass of the first peak in a doublet and ΔM is the difference in the masses of the two peaks. An increase in the value of R (denoting an increase in resolution) indicates an increase in the ability to distinguish between very nearly identical masses. Of the several mass spectrometers mentioned, the double-focusing type affords the greatest mass spectral resolution, sometimes exceeding 100,000. At this degree of resolution, masses appearing at m/e 99,999 and m/e 100,000 would be distinguishable. An instrument capable of such high resolution is of course very complex and expensive and thus would be used only when such high resolution is mandatory for effective analysis. In contrast, a quadrupole mass spectrometer is much simpler to operate and less expensive but can provide only low resolution ($m/\Delta m$ = 500 to 1000 typically).

Detection of the ions that have been separated is accomplished most often by use of an electron multiplier, of which, again, various types are in use. An electron multiplier produces current amplification of 10^3 to 10^8 with very low noise level and with negligible time constant or signal broadening. The amplified analog signal resulting from the ion impacting on the electron multiplier is finally routed to one of several possible data acquisition devices; among those often used are the oscillographic recorder, the analog recorder, a pulse counting device, or the digital computer.

The data from a mass spectrometer consist, in the analog format, of a spectrum of peaks (the mass spectrum). The position of each peak on the horizontal axis of a graphic display indicates its m/e ratio whereas the amplitude of each peak indicates the number of ions (or abundance) of that m/e. The data may also be displayed digitally in tabular form.

If more than one compound enters the mass spectrometer at a given time, then the masses detected are generally attributable to any or all of the compounds. Because it is difficult, and sometimes impossible, to interpret the mass spectra obtained for mixtures of organic compounds, there is great advantage in admitting the compounds separately. Thus a gas chromatograph is used to introduce the separated components of a mixture sequentially into the mass spectrometer. The following is a simplified description of a coupled GC-MS system.

Gas Chromatography/Mass Spectrometry (GC-MS) Systems

In considering the coupling of the gas chromatograph to a mass spectrometer, one should recall that the source, analyzer, and detector of the spectrometer are all typically maintained at pressures below 10^{-5} mm. Therefore, unless the mass spectrometer is equipped with a very high-capacity pumping system, the gaseous effluent from a gas chromatographic column cannot be admitted directly to the mass spectrometer source because this would increase the pressure to a level that would prevent satisfactory operation. Therefore, coupling is generally achieved by use of an intermediate device to reduce the rate of flow of the sample and carrier gas stream. For this purpose several types of devices (called "separators") are used to achieve partial separation of the carrier gas (typically helium) from the gaseous sample molecules. Among these devices are (1) a porous barrier or effluent splitter, (2) a jet/orifice separator, and (3) a molecular separator that includes a permeable membrane. Some gas chromatograph-mass spectrometer systems feature a direct coupling of the gas chromatograph with the mass spectrometer by means of a very high capacity pumping system.

A system that couples a chromatograph with a mass spectrometer is a very powerful analytical tool, the only system that can provide definitive analysis of complex chemical mixtures. The separation capabilities of the gas chromatograph are complimented by the inherent specificity and sensitivity of the mass spectrometer. During analysis of a complex mixture, the components are separated gas chromatographically; each eluted component then passes through the interface (separator) and into the mass spectrometer, which provides and records a mass spectrum. Typically, the analysis of a mixture could yield several hundred mass spectra, each containing 100 to 200 mass peaks. Therefore, the computer is an ideal means of acquiring the mass spectra, reducing the data (converting the acquired data to actual mass spectra by comparison with calibrated reference files), and displaying the data. The minicomputer is an essential component of a modern GC-MS system because the analyses generate such sizable quantities of data. Use of a minicomputer can afford other advantages; for example, the computer can be programmed to control the mass spectrometer so that it monitors only selected masses typical of the compounds of interest. The computer also can be programmed to allow monitoring of different masses (corresponding to different compounds) at different gas chromatographic retention times.

ANALYTICAL BACKGROUND

Analytical methods for detecting TCDD's in various types of samples involve extensive sample preparation procedures followed by highly complex instrumental analysis. This section discusses various approaches to the detection and quantitative measurement of TCDD's, which had been used prior to the inception of the present study in 1978.

Sample Preparation

Because TCDD's may be found in a variety of matrices, many different sample extraction/preparation methods have been developed. Although they differ in complexity, most of these methods may be classified into two major categories: first, those characterized by a highly basic extraction step, and second, those involving only neutral extraction. The neutral extraction technique was developed to preclude the possibility that treatment with a strong base might generate compounds that could form chlorinated dioxins in the mass spectrometer. Following extraction, the sample preparation steps are similar for both techniques, differing only in the method of application and complexity. Both extraction procedures are described in detail below.

Basic Extraction Method—

Historically, basic extraction methods were first developed for the determination of TCDD's in environmental samples (Crummet and Stehl 1973; Baughman and Meselson 1973a; Baughman and Meselson 1973b). Such sample preparation techniques begin with digestion of a sample aliquot using alcohol and a strong base. This is followed by a series of organic solvent extractions to separate the TCDD's from the alkaline mixture. Solvents such as ethanol, hexane, petroleum ether, and methylene chloride have been used, either singly or in combination. The solvent extracts are combined and then subjected to a series of washings with distilled water and strong acid. The washed extract is then treated to remove all traces of water and passed through one or more chromatographic columns for removal of some co-extractants, primarily polar compounds. Instrumental analysis follows.

An example of a typical basic extraction/preparation technique for nonfat tissue consists of heating 10 g of sample with 10 ml of ethanol and 20 ml of 40 percent potassium hydroxide solution for 30 minutes. After the solution cools, an additional 10 ml of ethanol is added and the solution is extracted with four 10-ml portions of hexane. The preparation procedure consists of washing the combined hexane extracts with concentrated sulfuric acid until the acid fraction becomes only slightly colored. The acid wash is followed by a 10-ml water wash, followed by evaporation to dryness at room temperature with a stream of dry air. The sample is then redissolved in hexane and further purified by elution chromatography using sorbents such as alumina, silica gel, or Florisil, either singly or in combination. The final eluate is concentrated prior to analysis.

Neutral Extraction Method—

The neutral extraction and preparation technique was originally developed by O'Keefe, Meselson, and Baughman (1978). Albro and Corbett (1977) describe an alternative neutral extraction method. A typical neutral extraction technique for analysis of TCDD's consists of extracting the sample with 10 ml of hexane. The hexane solution is then chromatographed with a magnesia-Celite 545 column, an alumina column, an alumina minicolumn, and finally a Florisil minicolumn. The Florisil column is eluted with methylene chloride, and the eluate is concentrated in preparation for analysis. It has been asserted that neutral extraction methods are particularly effective for fish tissues and human milk (O'Keefe, Meselson, and Baughman 1978; Harless and Dupuy 1979).

Chemical Composition of Extracts—

The sample preparation techniques described above are useful for destroying the integrity of the sample matrix and yield a small volume of organically miscible/soluble residue. The net effect of these clean-up procedures is the enrichment of the TCDD's relative to the natural components of the sample matrix, as well as other chlorinated environmental contaminants such as PCB's and DDE.* The latter compounds are often present in the sample in significantly greater concentrations than the TCDD's (larger by a factor of 10^6) and, therefore, may not be completely removed from the extract at this point. In addition, it is unlikely that the forgoing procedures result in separation of 2,3,7,8-TCDD from its other 21 TCDD isomers which may have been present in the sample.**

Consequently, detection and quantitation of TCDD's in general and 2,3,7,8-TCDD in particular in this "enriched" but still rather chemically complex extract can only be accomplished by using a highly specific and sensitive instrumental method. The method of choice, and that described below, is coupled gas chromatography-mass spectrometry.

Gas Chromatographic and Mass Spectrometric Methods of Analysis

Because of its ready availability and relative ease of application, gas chromatography has been extensively used for the detection and quantitation of TCDD's (Elvidge 1971; Williams and Blanchfield 1971; Firestone et al. 1972; Williams and Blanchfield 1972; Crummett and Stehl 1973; Edmunds, Lee, and Nickels 1973; Webber and Box 1973; Buser 1976; Bertoni et al. 1978). In many instances, the authors

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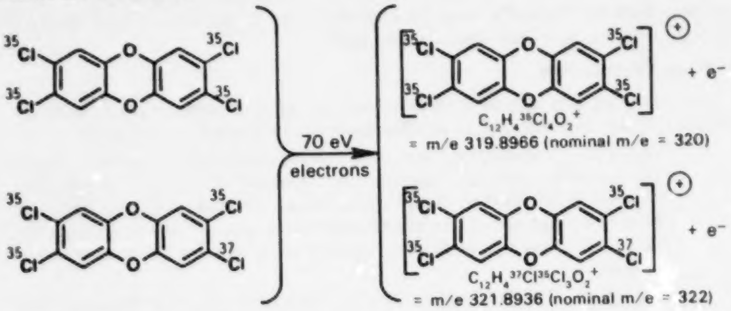
*DDE, or 2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethylene, is commonly found in environmental samples; it is a degradation product of the pesticide DDT.

**Subsequent to the completion of the work described herein, reports have appeared in the literature which describe methods for synthesis and isolation of the 22 TCDD isomers (Nestrick 1979; Dow 1980). Using such new analytical procedures, it is now possible to isolate and quantitatively determine 2,3,7,8-TCDD in environmental samples even in the presence of the other 21 isomers.

cited above have found that the chromatographic methods lack the required specificity for determining TCDD's in complex samples. Consequently these researchers and others have sought more sensitive and specific methods of detection.

At present the analytical method which is almost exclusively used for the detection and quantitation of TCDD's is coupled gas chromatography-mass spectrometry or GC-MS (Crummett and Stehl 1973; Tiernan et al. 1975; Taylor et al. 1975; Buser and Bosshardt 1976; Harless 1976; Buser 1977; Gross 1978).

GC-MS is the only known method that can provide very high sensitivity as well as the required selectivity for TCDD's. A particularly sensitive and specific GC-MS technique which has been used entails low-resolution selective ion monitoring. In the case of TCDD's, fragment ions at nominal m/e 320 and m/e 322, as shown below, are monitored.


35Cl
70 eV
electrons
+ e⁻
$C_{12}H_4{}^{35}Cl_4O_2{}^+$
= m/e 319.8966 (nominal m/e = 320)
35Cl
37Cl
+ e⁻
$C_{12}H_4{}^{37}Cl^{35}Cl_3O_2{}^+$
= m/e 321.8936 (nominal m/e = 322)

The intensities of these ions are recorded as the TCDD's elute from the gas chromatograph. The ratio of the intensities of m/e 320 to m/e 322 is a characteristic indicator of TCDD's. Unfortunately, other compounds which may also be present in the sample extract can also give rise to mass spectral ions at the same nominal masses (m/e 320 and m/e 322) as TCDD's. Two approaches can minimize this problem.

The first approach utilizes high resolution mass spectrometry ($M/\Delta M > 9000$) to increase the selectivity. The ions appearing under low-resolution MS conditions at nominal mass 322 may be produced from TCDD's which have $C_{12}H_4Cl_4O_2$ as their elemental composition and thus have an "exact" mass of 321.8936. Interfering ions such as pentachlorinated biphenyls may also appear at nominal mass 322, but their elemental composition is $C_{12}H_3Cl_5$, and therefore they have an "exact" mass of 321.8677. Thus, using high-resolution MS these ions of slightly different mass are distinguishable, and so the dioxin component having the exact mass of 321.8936 can be reliably measured. Conceivably, ions having the $C_{12}H_4Cl_4O_2$ composition can be produced from other compounds, but proper selection of chromatographic procedures maximizes the possibility of separating such compounds from TCDD's. The achievement of detection limits in the low-ppt range at high MS resolution generally requires the use of data acquisition methods which entail signal averaging (Shadoff and Hummel 1978; Gross 1978; Taylor et al. 1976).

A second approach to the problem of separating TCDD's from closely related interferences makes use of low-resolution mass spectrometry but incorporates a more selective separation step prior to the mass spectrometric analysis. Capillary column gas chromatography is useful for this purpose (Buser 1977), but liquid chromatography followed by capillary column gas chromatography has proved even more fruitful (Nestrick, Lamparski, and Stehl 1979; Dow 1980).

In both the GC-high-resolution and the GC-low- resolution mass spectrometric methods, internal standards are frequently used for the quantification of TCDD's. The analytical method developed in the present study utilizes an internal standard, namely $^{37}Cl_4$-2,3,7,8-TCDD.

ANALYTICAL METHOD*

The analytical procedure ultimately developed and described herein for determination of TCDD's in various industrial process waste samples utilizes two separate GC-MS systems. A gas chromatograph coupled to a low-resolution quadrupole mass spectrometer (GC-QMS) is used for preliminary identification of TCDD's in the extracts of the waste samples. A second apparatus coupling a gas chromatograph and a high-resolution mass spectrometer (GC-MS-30) is used to confirm the results obtained with the GC-QMS technique. The analysis method entails two steps, sample preparation and instrumental analysis, as described below. It should be emphasized that, even with the elaborate separation techniques employed here, the 2,3,7,8-TCDD isomer is still not resolved from the other TCDD isomers if these are present in the sample extracts. As a result, the quantitative data obtained here for TCDD's must be considered an upper limit rather than an absolute level for any individual TCDD isomer.

Sample Preparation

The following procedures were developed as an approach to preparation of industrial waste samples and have been successfully applied in this study.

1. Place a 2.0 g aliquot of the sample in each of the two extraction vessels. To each aliquot, add an appropriate quantity of $^{37}Cl_4$-2,3,7,8-TCDD dissolved in "distilled-in-glass" benzene as an internal standard. Spike one of the two aliquots with an additional known quantity of authentic native 2,3,7,8-TCDD at a concentration equal to the nominal amount expected in the sample.
2. Add 30 ml "distilled-in-glass" petroleum ether to each sample and mix thoroughly.
3. Extract each organic solution with 50 ml of double-distilled water and discard the aqueous layer.
4. Extract each solution with 50 ml of 20 percent potassium hydroxide and discard the aqueous basic layer.
5. Extract each solution with 50 ml of double-distilled water and discard the aqueous portion.
6. Extract each solution with 50 ml of concentrated sulfuric acid and discard the aqueous acidic layer.
7. Repeat step 6 until the acid layer is nearly colorless.
8. Extract each organic solution with 50 ml of double-distilled water and discard the aqueous layer.
9. Dry each organic solution over anhydrous sodium sulfate.
10. Quantitatively transfer each organic solution to another vessel, and concentrate to a volume of approximately 1 ml by passing a stream of purified nitrogen over the surface of the liquid while applying gentle heat (50° C) to the vessel.
11. Construct a chromatography column for each sample by packing a disposable glass pipette (I.D. = 0.8 cm) with glass wool and 2.8 g of Woelm basic alumina (previously activated by maintaining it at 600° C for a minimum of 24 hours, then cooled in a dessicator for 0.5 hour prior to use).
12. Quantitatively transfer each concentrated organic solution to the top of a column.
13. Elute each column with 10 ml of 3 percent "distilled-in-glass" methylene chloride in "distilled-in-glass" hexane, and discard the entire column effluent.

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*This section presents the analytical method only; discussion of development of the method follows in the next subsection.

14. Elute each column with 20 ml of 20 percent methylene chloride in hexane and collect the eluate in four 5-ml fractions.
15. Elute each column with 10 ml of 50 percent methylene chloride in hexane and retain the entire column eluate for analysis.
16. Elute each column with 3 ml of 50 percent methylene chloride in hexane and retain the eluate for analysis.
17. Concentrate all six fractions in benzene to an appropriate volume (usually 0.1 to 1.0 ml) and proceed with analysis.

Instrumental Analysis

The application of GC-MS instrumentation methods for analysis of TCDD's requires knowledgeable and experienced personnel, dedication of the equipment, and significant capital and operating costs. The requirement for detecting low ppt levels of TCDD's in these analyses necessitates such a sensitive and selective analytical method. Because this is currently the only known method which meets these criteria, the relatively high expense is unavoidable.

The following is a brief description of the instrumentation required for the analytical prodedures developed herein.

GC-QMS System—

The GC-QMS system consists of a Varian Model 2740 Gas Chromatograph coupled directly (no helium separator is required) to an Extra-nuclear Quadrupole Mass Spectrometer. The GC was adapted to include a sophisticated system of remotely actuated high-temperature switching valves (Valco Co.) and Granville-Phillips molecular leak valves, so that the column effluent could be readily regulated (Tiernan et al. 1975a; Erk, Taylor, and Tiernan 1978).

With this arrangement, the total column effluent can be directed into the mass spectrometer ion source, or the effluent flow can be split, one portion going to the ion source and the other to a gas chromatographic detector, as desired. The use of a differential high-speed pumping system on the source vacuum envelope permits introduction of as much as 65 ml/min of effluent from the gas chromatograph into the mass spectrometer ion source. Admitting the total chromatograph effluent into the mass spectrometer source enhances the sensitivity of the analysis.

For purposes of instrument control and data acquisition, the GC-QMS system is coupled to an Autolab System IV Computing Integrator. Additional capacity for off-line data reduction is available with a Hewlett-Packard 2116C Minicomputer, which is programmed to accept data (punched paper tape) from the system when necessary.

GC-MS-30 System—

The GC-MS-30 system used in these studies consists of a Varian 3740 Gas Chromatograph coupled through an AEI silicone membrane separator to an AEI MS-30 Double-Focusing, Double-Beam Mass Spectrometer. The mass spectrometer is equipped with a unique electrostatic analyzer scan circuit developed by Wright State University, which permits the monitoring of as many as four mass peaks, essentially simultaneously, by rapidly and sequentially stepping and switching between the masses of interest, while maintaining picogram sensitivity for TCDD's. The data are recorded by use of a Nicolet 1074 Signal Averaging Computer.

Sample Analysis—

Analysis consists of three steps as described below.

1. Analyze each eluate fraction (collected in the elution chromatography separation of the sample) on the low-resolution GC-QMS, using the following operating parameters:

Varian 2740 Gas Chromatograph

Column: 2 m × 3 mm I.D. glass packed with 3 percent OV-7 on Gas Chrom Q

Carrier gas: Helium at 65 ml/min (the total chromatographic column effluent is admitted to the mass spectrometer ion source)

Temperatures:
Injector: 255° C
Column: 275° C
Transfer line: 295° C

Quadrupole Mass Spectrometer

Ionizing voltage: 23.5 eV

Multiplier: 3200 V

Resolution: 1:350

Source envelope pressure: 1.4×10^{-4} torr

Analyzer envelope pressure: 8.0×10^{-6} torr

Masses monitored: m/e 320, 322

Source temperature: 250° C

Analyzer temperature: 120° C

2. Confirm any samples showing positive levels of TCDD's on the low-resolution GC-QMS by analysis of the corresponding eluate fractions using high-resolution GC-MS-30 and the following operating parameters:

Varian 3740 Gas Chromatograph

Column: 1.8 m × 2 mm I.D. coiled glass column packed with 3 percent Dexsil 300 on Supelcoport (100/120 mesh)

Carrier gas: Helium at a flow rate of 30 ml/min

Temperatures:
Injector: 250° C
Column: 240° C
Transfer line: 285° C

AEI MS-30 Mass Spectrometer

Resolution: 1:12,500

Ionizing voltage: 70 eV

Masses monitored: m/e 319.8966, 321.8936, 325.8805, and 327.8846

Temperatures:
Membrane separator: 215° C
Transfer line: 270° C
Source: 250° C

3. Determine the overall recovery of the analytical prodedure by measuring the amount of internal standard ($^{37}Cl_4$-2,3,7,8-TCDD) recovered.

DISCUSSION AND RESULTS

For use in developing and demonstrating the analytical methodology for determination of ppt levels of TCDD's in process wastes and related materials, samples were provided that were representative of wastes from several different industrial chemical processes that might be expected to generate chlorodioxins. The samples were obtained by the U.S. EPA from plants manufacturing trichlorophenol, pentachlorophenol, and hexachlorophene, and from plants processing wood preservatives. Initially, the nature and identity of each sample were unknown to the Wright State investigators, although information was made available early in the program about two of the samples originating from trichlorophenol manufacturing processes. Subsequently, identifying data on most of the remaining samples were obtained and are summarized in Table 22.

TABLE 22. SAMPLES USED IN DEVELOPMENT OF ANALYTICAL METHOD FOR TCDD'S IN INDUSTRIAL WASTES

EPA No.	Sample type	Source and identity of sample
CO4130	Liquid slurry	Givaudan: aqueous slurry of hexachlorophene
CO4131	Solid	Givaudan: activated clay filter cake from hexachlorophene manufacturing
CO4132	Liquid	Givaudan: ethylene dichloride recovery solution from hexachlorophene manufacturing
2	Liquid/solid	Transvaal: still bottom from trichlorophenol (TCP) manufacturing
3	Slurry	Transvaal: cooling tank bottom from TCP manufacturing
4	Slurry	Transvaal: discharge line from TCP manufacturing
5	Liquid/solid	Transvaal: sludge from TCP manufacturing
6	Liquid	Transvaal: type unknown; presumably TCP process sample
12700	Liquid/solid	Reichold Chemical: sludge from intake of settling pond, pentachlorophenol (PCP) manufacturing
12701	Liquid	Reichold Chemical: sludge from discharge of settling pond, PCP manufacturing
12702	Solid	Reichold Chemical: PCP manufacturing
11020	Liquid/solid	Baxter: retort solids residue from wood preserving
11021	Liquid	Baxter: storage tank solution from wood preserving
11022	Liquid/solid	Baxter: cooling water solids from wood preserving
11023	Solid	Baxter: treated wood from wood preserving
11024	Solid	Baxter: soil from neighborhood of wood preserving plant
11025	Solid	Baxter: sludge from wood preserving

Because still bottom samples collected at a trichlorophenol manufacturing plant were considered of major interest, a sample of this type (EPA sample 2) was selected for use in preliminary investigations.

The initial approach to analytical method development, based on the experience of Wright State personnel in chlorodioxin analysis, is outlined below.

1. If the sample is solid, dissolve a portion in an immiscible combination of aqueous and organic solvents, such as water and petroleum ether. If the sample is a liquid, extract a portion of the material with a similar water-organic solvent system. In the absence of any prior knowledge about the content of TCDD's in a given sample, the quantity to be extracted must be selected on the basis of sensitivity of the overall technique (as indicated by previous experience) and the desired limits of detection.
2. Separate the aqueous component of the sample-solvent mixture from the organic phase, and discard the aqueous portion.
3. Extract the organic fraction with sequential washes of acid, water, base, water, acid, and water (in that order), and discard the washes.
4. Concentrate the remaining organic phase to near dryness and elute through an alumina column, using appropriate solvents to separate the TCDD's and other sample components.
5. Concentrate the fraction containing TCDD's and subject it to preliminary screening analysis by use of the GC-QMS system, operated in the selected-ion monitoring mode and adjusted to detect m/e 322 and m/e 320, the two most abundant peaks in the isotopic molecular ion cluster of 2,3,7,8-TCDD.
6. If the initial screening indicates a positive level of TCDD's, then the level must be confirmed and quantitated by use of the GC-MS-30 system.

This approach was used in analysis of sample 2. Subsequent modifications of this initial procedure and other observations are discussed in following subsections.

Developing Sample Preparation Technique

Four aliquots of sample 2 were extracted with a mixture of water and petroleum ether. The aqueous portion was discarded, and each organic fraction was washed successively with acid, water, base, water, acid, and water. The samples were then concentrated and transferred to a 2.8 g Woelm basic alumina column (length 12 cm, I.D. 0.8 cm).

Large quantities of a white crystalline substance appeared in the column eluate. The column apparently was overloaded owing to the large quantity of this material present in the sample. This substance possibly accounted for interference in the mass chromatogram (Figure 37). Adjustments of the column chromatography procedure were therefore made in an effort to eliminate this crystalline contaminant in the fraction containing the TCDD's.

A solvent screening study was done to evaluate the solubility of the contaminant and the potential for its removal from the sample matrix. Results are as follows:

Solvent tested	Solubility of contaminant
100% methanol	Slight solubility
3% methylene chloride in hexane	Solubility slightly greater than in 100% methanol
25% carbon tetrachloride in hexane	Solubility slightly greater than in 3% methylene chloride in hexane
100% methylene chloride	Completely soluble

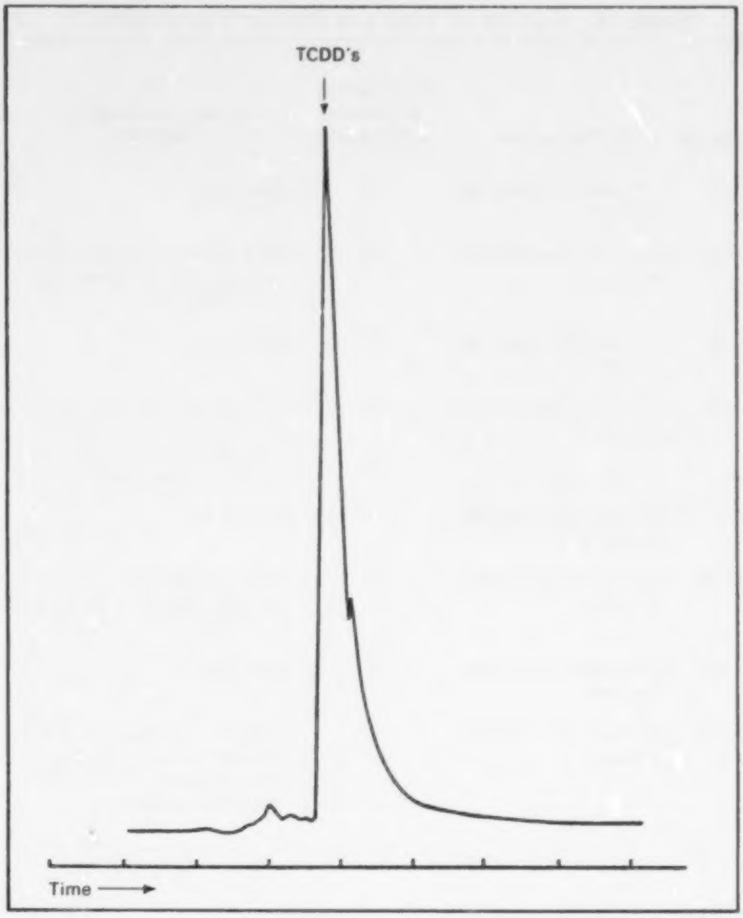

Figure 37. Mass chromatogram of extract of sample 2, at m/e 322 obtained with GC-QMS.

Next, elution characteristics of the alumina column were evaluated. Table 23 presents the solvents and the discrete fractions collected in determining the elution characteristics of the Woelm basic alumina column.

Selection of the solvents and the eluate fractions was based on earlier experience of Brehm Laboratory personnel in column chromatography with similar sample matrices.

The eluate fractions were analyzed for TCDD's by use of the GC-QMS system. The results, presented in Table 24, show clearly that the best elution sequence involves the use of 10 ml of 3 percent methylene chloride in hexane, followed by 18 ml of 20 percent methylene chloride in hexane. This sequence yields TCDD's in a well-defined fraction containing few other contaminants. Use of all the other solvent pairs yielded fractions that generated interferences in the dioxin mass chromatogram which were as great as those shown in Figure 37 or greater.

TABLE 23. ELUTION OF TCDD'S IN EXTRACTS OF SAMPLE 2

Set no.	Eluting solvent	Total volume of column effluent (ml)	Volume of fraction (s) collected
A1	3% methylene chloride in hexane	10	total 10 ml
A2	50% methylene chloride in hexane	13	1st 5 ml in one fraction; 6th through 13th ml in separate 1-ml fractions
B1	3% methylene chloride in hexane	10	total 10 ml
B2	20% methylene chloride in hexane	18	1st 5 ml in one fraction; 6th through 13th ml in separate 1-ml fractions; 14th through 18th ml in one fraction
C1	25% carbon tetrachloride in hexane	10	total 10 ml
C2	50% methylene chloride in hexane	13	1st 5 ml in one fraction; 6th through 13th ml in separate 1-ml fractions
D1	25% carbon tetrachloride in hexane	10	total 10 ml
D2	20% methylene chloride in hexane	18	1st 5 ml in one fraction; 6th through 13th ml in separate 1-ml fractions; 14th through 18th ml in one fraction

Application of Initial Procedure to EPA Samples—

The extraction and sample preparation procedure developed for sample 2 was applied to ten of the other industrial samples supplied by EPA. In these analyses some interferences were still present in the extract fraction which was thought to contain the TCDD's; the interferences resulted in a higher minimum detection limit (ppb) than was desired. Portions of these samples were also spiked with known quantities of 2,3,7,8-TCDD so that recoveries for the procedure could be determined. The recovery in GC-QMS analysis of sample 2 was 127 percent.

Surprisingly, in analysis of the other ten samples by the same procedure, none of the added 2,3,7,8-TCDD was recovered. The same procedure was then applied in analyses of spiked aliquots of these samples, but this time all the eluate fractions from the alumina columns were retained and analyzed for TCDD's. Again, no 2,3,7,8-TCDD was detected. It was necessary to further investigate the sample preparation procedures.

Optimizing Sample Preparation Procedure—

Another sample (CO4131) was subjected to the general preparation procedure already described, up to the point of elution of the column. Then the sample was

TABLE 24. CONTENT OF TCDD'S IN COLUMN FRACTION FOR SAMPLE 2[a]

Solvent set no.	Eluate fraction no.[b]																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	TCDD's detected																	
A1	–*	–*	–*	–*	–*	–*	–*	–*	–*	–*	o	o	o	o	o	o	o	o
A2	+*	+*	+*	+*	+*	+*	+*	+*	+	–	–	–	–	o	o	o	o	o
B1	–	–	–	–	–	–	–	–	–	–	o	o	o	o	o	o	o	o
B2	+*	+*	+*	+*	+*	+	+	+	+	+	+	+	+	+	+	+	+	+
C1	o	o	o	o	o	o	o	o	o	o								
C2	+*	+*	+*	+*	+*	+*	+*	+*	+*	+*	+*	+*	+*	o	o	o	o	o
D1	o	o	o	o	o	o	o	o	o	o								
D2	+*	+*	+*	+*	+*	+*	+*	+	+	+	+	+	+	+	+	+	+	+

a—Aliquots of EPA sample 2.
b—Fraction numbers refer to those collected from each of the columns, as indicated in Table 23.
+ = TCDD's present in fraction.
– = No TCDD's detected in fraction.
o = Fraction not analyzed.
* = Two or more peaks evident in mass chromatogram near 2,3,7,8-TCDD retention time.

spiked with a large quantity of 2,3,7,8-TCDD by introducing it directly onto the alumina column. The column elution characteristics were then evaluated as before and the results are shown in Table 25. This procedure was repeated for all other samples and their column elution profiles were determined.

TABLE 25. RECOVERY OF 2,3,7,8-TCDD SPIKE FROM ELUATES OF SAMPLE CO4131

Solvent	No. of fractions collected	Volume of each fraction	Action	Results
10 ml 3% methylene chloride in hexane	1	10 ml	Discarded	
20 ml 20% methylene chloride in hexane	4	5 ml	Analyzed by GC-QMS	No 2,3,7,8-TCDD
10 ml 50% methylene chloride in hexane	1	10 ml	Analyzed by GC-QMS	80% 2,3,7,8-TCDD recovered

This study indicated that a general extraction and preparation procedure must include a provision for assessing the elution characteristics of the alumina column for each type of sample matrix. Apparently, each type of sample conditions or deactivates the column in a manner peculiar to its matrix, and this conditioning, in turn, determines the elution characteristics of TCDD's, which may differ markedly in different sample types.

Analytical Procedure

Research workers in several laboratories, including the Brehm Laboratory, have analyzed various types of samples for dioxin content. Generally, the analytical approach to determining a chlorinated hydrocarbon of this type in a complex sample matrix has involved quantitation of the chlorocarbon by use of electron capture-gas chromatography (EC-GC) or gas chromatography-mass spectrometry (GC-MS). The studies at Brehm Laboratory entailed use of GC-MS and high-performance liquid chromatography (HPLC).

GC-MS System—

As described in the subsection entitled "Analytical Method," the GC-QMS system was used for initial detection of TCDD's in the fractionated sample. Then GC-MS-30 was used to confirm the positive levels of TCDD's detected in the GC-QMS.

In one procedural modification, a labelled internal standard, $^{37}Cl_4$-2,3,7,8-TCDD, was added to all samples. Also, the MS-30 high-resolution mass spectrometer was modified to permit essentially simultaneous step-scanning of four ions in the high-resolution mode. The ions typically monitored were:

m/e 319.8966,	a major molecular ion in the mass spectrum of 2,3,7,8-TCDD
m/e 321.8936,	a major molecular ion in the mass spectrum of 2,3,7,8-TCDD
m/e 325.8805,	a molecular ion indicative of interfering PCB's
m/e 327.8846,	a major molecular ion in the mass spectrum of $^{37}Cl_4$-2,3,7,8TCDD.

High-Performance Liquid Chromatography (HPLC)—

In earlier studies aimed at determining TCDD's in environmental samples, concern has been raised that the presence of the so -called predioxins (for example, polychlorinated phenoxyphenols) in the samples would lead to false positive determinations of TCDD's because the latter can be formed by cyclization reactions of the predioxins in the hot injection port of gas chromatographs. The present investigation ruled out potential false positive effects of predioxins by applying an HPLC analytical technique as a quality assurance measure. HPLC does not entail injection of the sample into a heated port and therefore minimizes the possibility of thermal cyclization of predioxins.

The HPLC instrument used in these studies is the Model LC 5021 Varian. This microprocessor-controlled HPLC is both completely automatic and programmable and incorporates a multiple solvent system. Three detectors are available: a fixed-wavelength UV (254 nm) detector, a variable-wavelength UV detector, and a flourescence detector. A cathode ray tube (CRT) keyboard unit displays operating parameters while a micropressor-based computing integrator (DCS-111L) stores the data and performs appropriate calculations. The parameters applicable to the instrument as it was used in this study are listed below:

Column:	DuPont Zorbax ODS (25 cm × 6.2 mm)
Temperature:	50° C
Starting pressure:	952 psig
Solvent:	100% methanol
Flow rate:	2.5 ml/min
Detector:	UV (235 nm)
Sensitivity:	0.02 absorbance units full scale/15 mg TCDD's

Upon injection of a 10 μl aliquot of the sample 2 extract into the HPLC, a chromatographic peak having a retention time which was the same as that observed with the 2,3,7,8-TCDD standard was observed. Representative HPLC chromatograms are shown graphically in Figures 38 and 39, and these results indicate a readily detectable level of TCDD's in the sample 2 extract. It is apparent that the TCDD's detected cannot have been formed by cyclization of predioxins.

Analytical Results—

Attempts were made to extract 15 of the 17 EPA samples by the procedures described in the subsection on the analytical method. The remaining two samples, 11023 and 12702, were not subjected to these methods. Sample 11023 was a section of wood, which the earlier experience of Wright State had shown is not amenable to a potassium hydroxide digestion process. Sample 12702 was not analyzed because of insufficient time during the contract period.

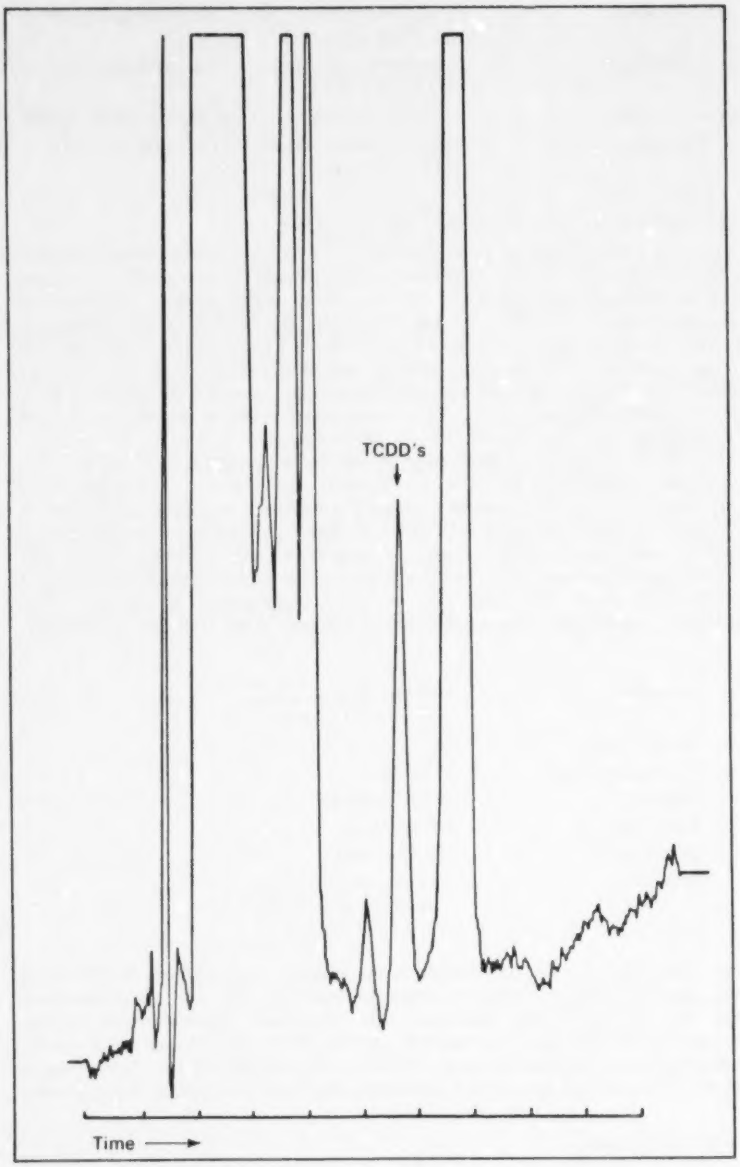

Figure 38. High pressure liquid chromatogram of sample 2.

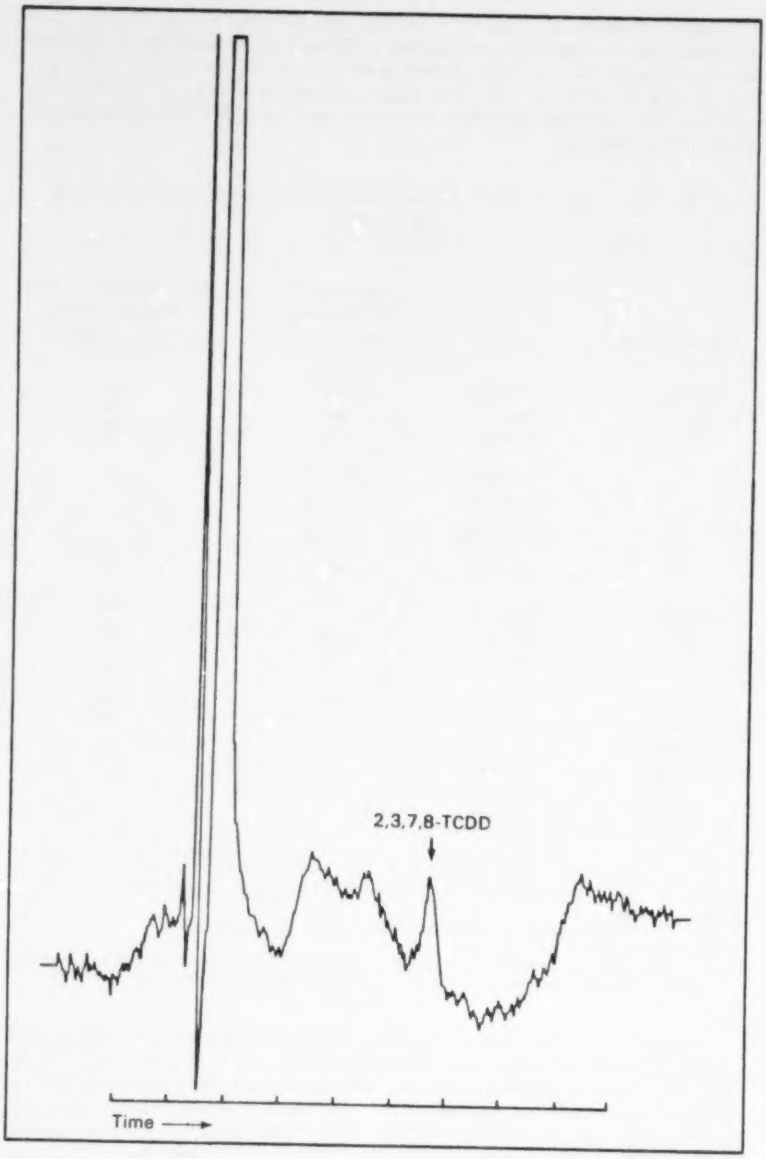

Figure 39. High pressure liquid chromatogram of 2,3,7,8-TCDD standard.

Twelve of the 15 samples were successfully analyzed by the Wright State procedure, with results as shown in Table 26. These data show that the procedure is applicable to samples exhibiting a wide range of concentrations of TCDD's from ppt to ppm (a factor of 10^6). For those samples in which no TCDD's were detected, the minimum detectable concentration of TCDD's was in the low ppt range (45 to 140 ppt).

TABLE 26. RESULTS OF GC-MS-30 ANALYSIS OF EPA SAMPLES FOR TCDD'S

EPA sample no.	Origin	Quantity of TCDD's found ng/g (ppb)	Minimum detectable concentration pg/g (ppt)
CO4130	Givaudan	ND[a]	140
CO4131	Givaudan	ND	70
CO4132	Givaudan	ND	50
2	Transvaal	40,000	e
3	Transvaal	675	e
3	Transvaal	22	e
5	Transvaal	70	e
6	Transvaal	ND	50
12700	Reichold	ND	80
12701	Reichold	ND	75
12702	Reichold	b	
11020	Baxter	ND	140
11025	Baxter	ND	45
11021	Baxter	c	
11022	Baxter	c	
11023	Baxter	b	
11024	Baxter	d	

a—ND: No TCDD's detected in excess of the minimum detectable concentration.

b—Not processed.

c—General procedure could not be successfully applied to these samples.

d—Not analyzed on GC-MS-30.

e—An exact minimum detectable concentration was not recorded for these analyses; however, the reported values for quantity of TCDD's found are well above the criterion of 2.5x noise.

Examples of mass fragmentograms obtained with the GC-MS-30 high resolution mass spectrometer are shown in the following figures. Figure 40 shows a four-ion step-scan mass fragmentogram of benzene, the solvent used for dilution of the final sample residue. Analysis of a solvent blank is repeated before analysis of each sample in order to ensure that no TCDD's are carried over in the injection syringe. Figure 41 illustrates similar data obtained from injection of a sample consisting of 50 pg of native 2,3,7,8-TCDD and 1 ng of $^{37}\mathrm{Cl}_4$-2,3,7,8-TCDD. Note that different attenuations have been applied to the various peaks displayed in Figure 41. Figures 42 and 43 demonstrate similar four-ion step-scan mass fragmentograms obtained for two of the EPA samples. Although the fragmentogram for sample 12700 shows peaks at m/e 319.8966 and m/e 321.8936, their intensities are not greater than 2.5 times the background; this is one of the

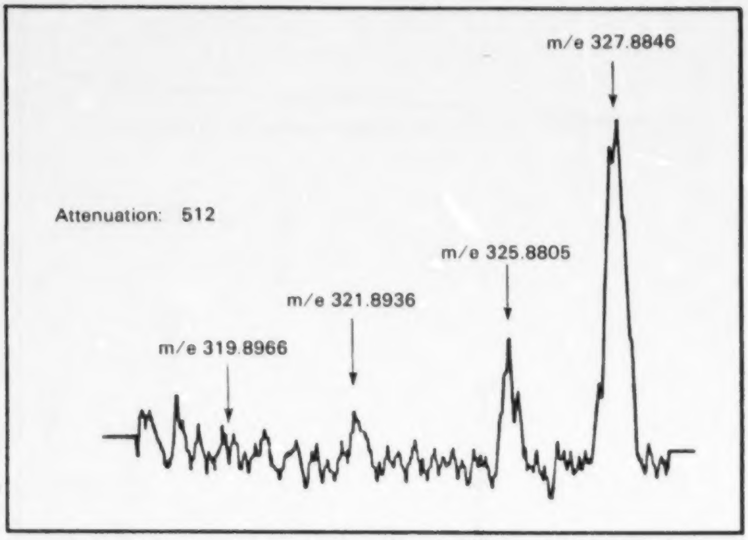

Figure 40. Four-ion mass fragmentogram of benzene solvent blank obtained with GC-MS-30.

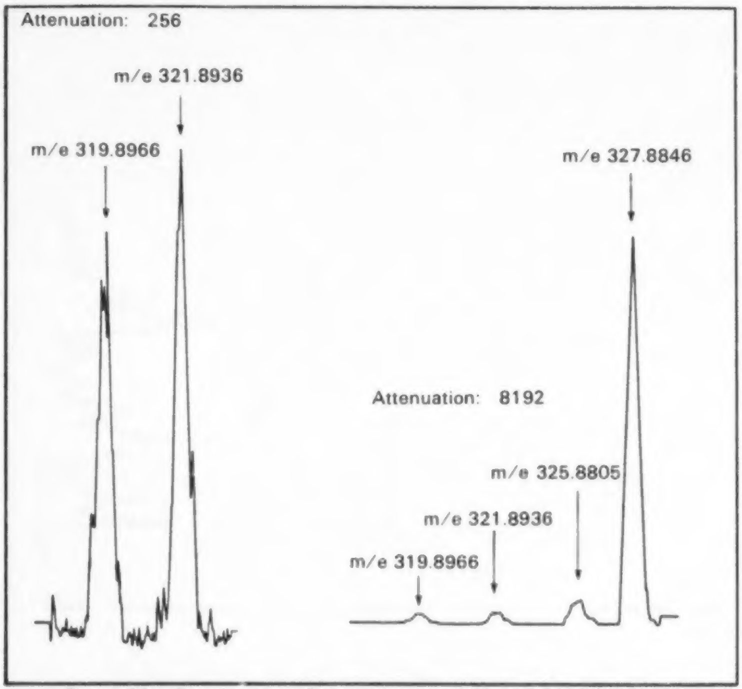

Figure 41. Four-ion mass fragmentogram of 50 pg 2,3,7,8-TCDD and 1 ng $^{37}Cl_4$-2,3,7,8-TCDD obtained with GC-MS-30.

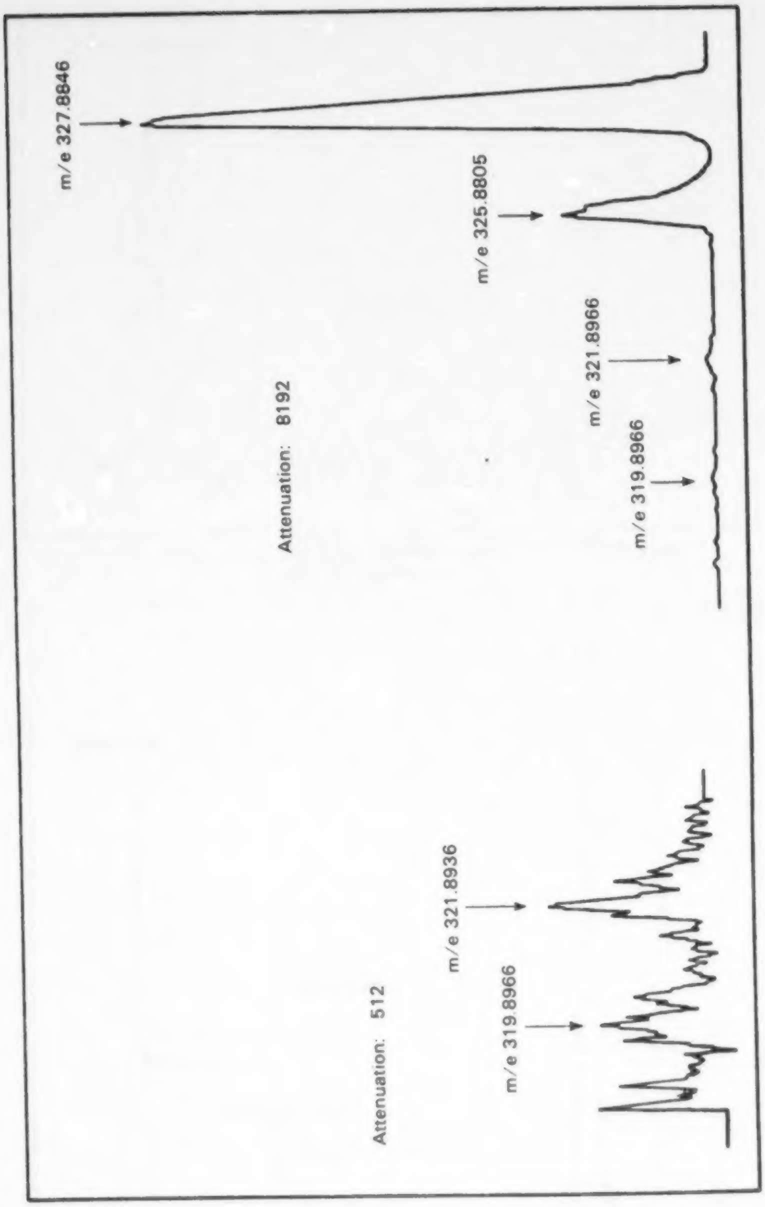

Figure 42. Four-ion mass fragmentogram of sample 12700 obtained with GC-MS-30.

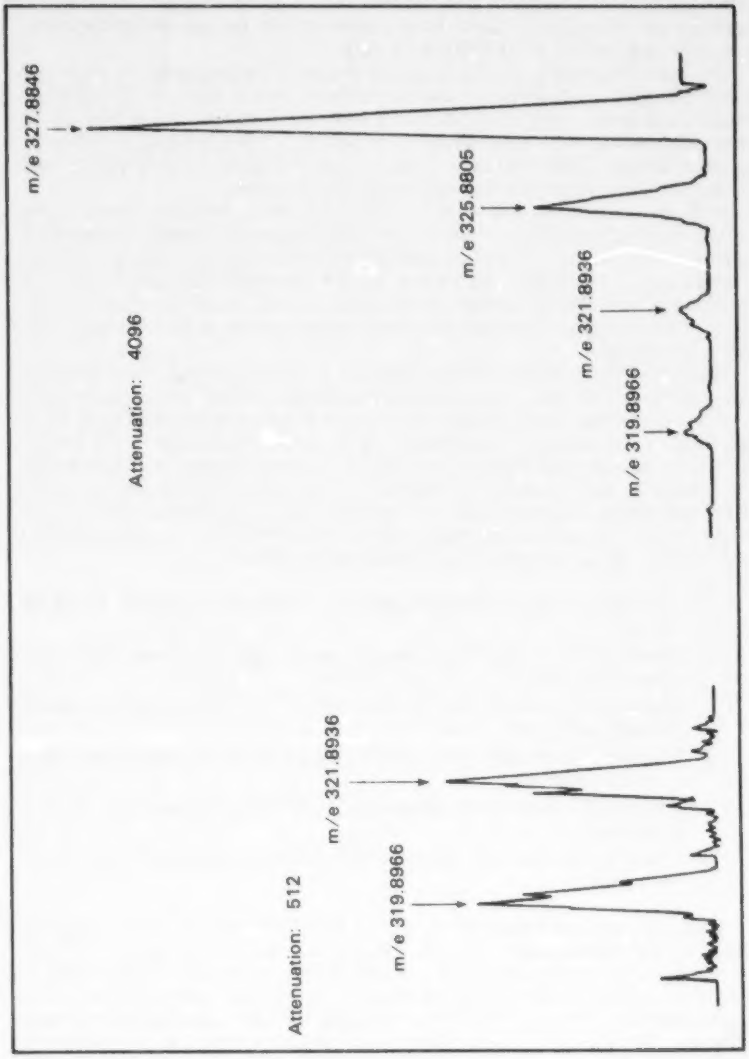

Figure 43. Four-ion mass fragmentogram of sample 5 obtained with GC-MS-30.

criteria applied for establishing the presence of TCDD's in a sample. Based on the recovery of $^{37}Cl_4$-2,3,7,8-TCDD from sample 12700, the minimum detectable concentration (MDC) of TCDD's is 80 pg/g.

The mass fragmentogram for sample 5 (Figure 43) shows peaks at both m/e 319.8966 and m/e 321.8936, and the intensities are well in excess of 2.5 times the background levels. After application of a recovery correction on the basis of the internal standard, these data indicate that sample 5 contains 70 pg TCDD's per gram of sample. Data similar to those shown in Figures 40 through 43 were obtained for the other samples analyzed in this program.

Analyses of samples 11021 and 11022 were not completed owing to the formation of an intractable emulsion at the petroleum/ether interface. Analysis of sample 11024 on the GC-MS-30 system was not attempted because a colored residue was visible in the final extract. Earlier experience had shown that such residues indicate that the sample extract contains gross quantities of compounds other than TCDD's, which lead to serious contamination of the high-resolution mass spectrometer.

All data in Table 26 were derived from analyses with the high resolution GC-MS-30 system. For each of the industrial process samples, the appropriate elution chromatogram fractions to be analyzed were determined in advance in a series of alumina column elutions using an aliquot of the sample spiked with 2,3,7,8-TCDD standard; these elutions were accomplished in a manner similar to that described for sample 2. These elution test samples were analyzed with the low resolution GC-QMS system. Data pertinent to the determination of the elution characteristics of TCDD's in the various samples are shown in Table 27. The fractions collected for each sample in the elution experiments are as follows:

1. Fraction I—First 5-ml portion eluted with 20 percent methylene chloride in hexane.
2. Fraction II—Second 5-ml portion eluted with 20 percent methylene chloride in hexane.
3. Fraction III—Third 5-ml portion eluted with 20 percent methylene chloride in hexane.
4. Fraction IV—Fourth 5-ml portion eluted with 20 percent methylene chloride in hexane.
5. Fraction V—First 10-ml portion eluted with 50 percent methylene chloride in hexane.
6. Fraction VI—Last 3-ml portion eluted with 50 percent methylene chloride in hexane.

These fractions were analyzed with the GC-QMS in reverse order, beginning with the last fraction and continuing backward until the quantity of TCDD's detected in the several fractions was a reasonably large percentage of that originally added as the spike, or until a fraction was reached that contained no TCDD's. The data in Table 27 show that TCDD's are completely eluted from all samples prior to Fraction VI. In most cases the bulk of the TCDD's appeared in Fraction V, although in samples 11020 and 11024 the TCDD's were detected in Fraction IV.

Table 28 summarizes the total recoveries of the added 2,3,7,8-TCDD spikes achieved by collecting the optimum column chromatography fractions of the various industrial process samples. These recoveries range from 60 to 102 percent, with a mean value of 85 percent.

Except for sample 2, all of the samples processed in this investigation were also spiked with $^{37}Cl_4$-2,3,7,8-TCDD. This compound was added as an internal standard in the analyses with the GC-MS-30 system. The mean recovery of $^{37}Cl_4$-2,3,7,8-TCDD for the samples analyzed herein was 74 percent with a standard deviation of 16.8 percent. The recovery data are shown in Table 29.

Confirmation of TCDD's in Sample 2—

Measurements in which m/e 320 and m/e 322 were monitored by the low-resolution GC-QMS system indicated that sample 2 contained approximately 40 μg TCDD's per gram of sample. The report of this high level of TCDD's prompted considerable concern both at EPA and state regulatory organizations.

This finding was also controversial because an earlier examination of this sample in an EPA laboratory had yielded no indication of the presence of TCDD's. It was obviously important, therefore, to more definitively confirm the initial Wright State analyses of sample 2; this was done by a procedure essentially the same as that which is described as the final method.

TABLE 27. TCDD ISOMER CONTENT OF COLUMN FRACTION SAMPLES SPIKED WITH 2,3,7,8-TCDD

EPA samples[a]	Eluate fraction[b]	Quantity of 2,3,7,8-TCDD added to sample (ng/g)	Quantity of 2,3,7,8-TCDD detected in fraction[c] (ng/g)	Minimum detectable concentration (ng/g)	Recovery (%)
CO4130	IV	10.42	ND	0.50	
	V		10.62		102
	VI		ND	0.50	
3	V	10.35	597		
	III	50.64	ND	3.00	
	IV		46		
	V		625		
	VI		ND	3.00	
12700	IV	12.14	ND	0.30	
	V		8.4		69
	VI		ND	0.57	
12701	IV	12.84	ND	0.28	
	V		10.12		79
11020	IV	9.86	0.56		6
	V		8.68		88
	VI		ND	0.23	
11024[d]	IV	3.71	0.29		8
	V		1.09		29
	VI		ND	0.08	
11025	IV	6.54	ND	0.14	
	V		5.63		86

a—See Table 22 for description of sample

b—Designation of eluate fractions:

III Third 5-ml aliquot eluted with 20% methylene chloride in hexane.
IV Fourth 5-ml aliquot eluted with 20% methylene chloride in hexane.
V First 10-ml aliquot eluted with 50% methylene chloride in hexane.
VI Last 3-ml aliquot eluted with 50% methylene chloride in hexane.

c—ND: no 2,3,7,8-TCDD detected in excess of the minimum detectable concentration.

d—Portion of sample was lost during preparation.

TABLE 28. RECOVERIES OF 2,3,7,8-TCDD-SPIKED SAMPLES FOLLOWING ALUMINA COLUMN CHROMATOGRAPHY

EPA samples	Quantity of 2,3,7,8-TCDD added (ng/g) (ppb)	Quantity of 2,3,7,8-TCDD detected (ng/g) (ppb)	Recovery (%)
C04130	10.4	10.60	102
4	12.0	8.40	70
5	12.2	11.00	90
6	10.4	9.70	93
12700	12.1	8.40	69
12701	12.8	10.10	79
11020	9.9	9.24	94
11024	3.7	1.38	37[a]
11025	6.5	5.60	86

a—Portion of sample lost during preparation.

TABLE 29. RESULTS OF GC-MS-30 ANALYSES OF SAMPLES SPIKED WITH $^{37}Cl_4$-2,3,7,8-TCDD

EPA samples	WSU samples	Quantity of ^{37}Cl-2,3,7,8-TCDD added (ng/g) (ppb)	Quantity of ^{37}Cl-2,3,7,8-TCDD detected (ng/g) (ppb)	Recovery (%)
C04130	B-001C	1.11	0.78	70
C04131	B-002A	0.93	0.91	98
C04132	B-003A	0.96	0.61	64
5	B-006A	1.21	0.48	40
6	B-007A	1.09	0.67	61
4	B-008A	1.09	0.75	69
12700	B-009E	1.23	1.06	86
12701	B-010E	1.29	1.14	88
11020	B-012F	1.19	0.93	78
11025	B-017B	0.67	0.58	86

a--Data for samples 2 and 3 are not included because the ratio technique could not be used with samples containing high levels of TCDD. Sample 11024 is also omitted because the extract was not clean enough for analysis by GC-MS-30.

The sample was extracted, and the extract was subjected to liquid chromatography preparation. As mentioned earlier, the fraction of sample 2 that was eluted from the alumina column with 20 percent methylene chloride in hexane was determined to contain the bulk of the TCDD's. Accordingly, this fraction was analyzed for TCDD's by the GC-MS-30 system operated in the dual-ion monitoring mode (m/e 319.8966 and 321.8936 were monitored). The resolution of the MS-30 mass spectrometer was adjusted to 1:12,500 for this measurement.

The dual-ion step-scan mass fragmentogram obtained with this sample extract is shown in Figure 44 and corresponding data obtained with an authentic 2,3,7,8-TCDD standard are shown in Figure 45. For EPA sample 2, the ratio of m/e 319.8966 to m/e 321.8936 in the mass fragmentogram is 0.79, while that for the 2,3,7,8-TCDD standard is 0.84. Both of these values agree well with the theoretically predicted ratio of these two peaks, 0.77, which is calculated on the basis of the relative abundance of ^{35}Cl and ^{37}Cl isotopes.

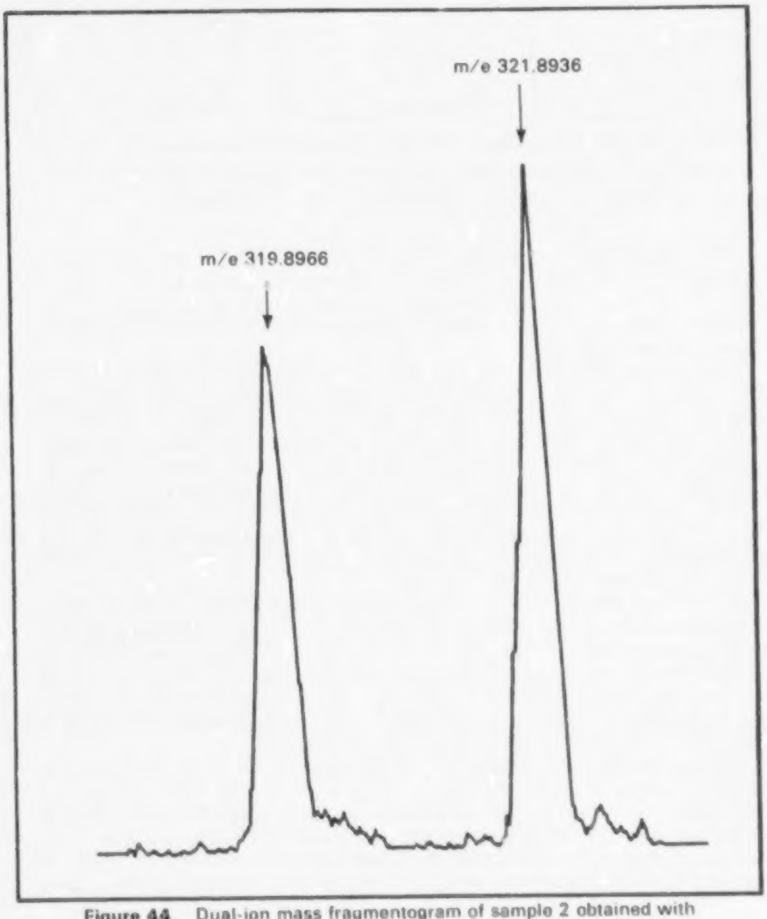

Figure 44. Dual-ion mass fragmentogram of sample 2 obtained with GC-MS-30, mass resolution 1:12,500.

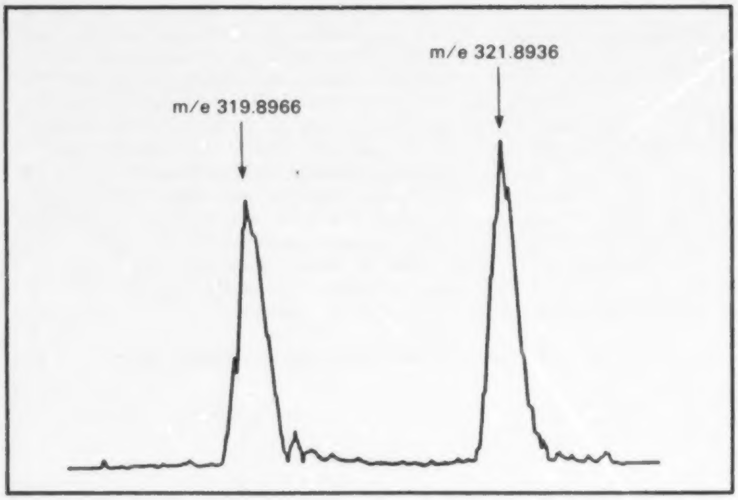

Figure 45. Dual-ion mass fragmentogram of 150 pg of 2,3,7,8-TCDD standard obtained with GC-MS-30, mass resolution 1:12,500.

Further confirmation that the unknown component in sample 2 is indeed a quantity of TCDD isomers is provided by the observation that the GC retention time of the unknown component was identical to that of the 2,3,7,8-TCDD standard. This criterion is applied in all determinations of TCDD's in Wright State's Brehm Laboratory.

The mass spectrometric resolution achieved in this program with the MS-30 Mass Spectrometer can be demonstrated experimentally by using the specialized step-scan circuitry developed by Wright State. The practical method of demonstrating the resolution is to obtain a narrow mass scan for a sample consisting of TCDD's in a mixture of other compounds that yield mass spectral ions whose mass is very close to that of TCDD's. In earlier studies we utilized a mixture of 2,3,7,8-TCDD, PCB's such as Aroclor 1254, and DDE[*] for this purpose. The latter compounds yield mass spectral peaks that are very near the mass of the TCDD's major ion (Aroclor 1254 m/e 321.8679, DDE m/e 321.9290, 2,3,7,8-TCDD m/e 321.8936).

In order to obtain ions of approximately equal intensity from all these compounds, however, the quantities of PCB and DDE must be quite large relative to the quantitiy of TCDD's. Figure 46 shows a typical mass fragmentogram obtained during this investigation in analyses of two mixtures of 2,3,7,8-TCDD and DDE and a mixture of Aroclor 1254, 2,3,7,8-TCDD, and DDE. On the basis of the data shown in Figure 46, the dynamic resolution of the mass spectrometer is calculated to be 14,000 with 20 percent valley definition.

The data on sample 2 which were described above were based on monitoring only m/e 320 and m/e 322 in the mass spectrum of TCDD's. Our earlier experience had shown that the low levels of TCDD's that are usually found in environmental samples (low ppt) permit monitoring of no more than four mass peaks for a single sample injection, even with the sophisticated step-scan techniques developed in Brehm Laboratory. In this instance, however, the level of TCDD's (40 ppm) in

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[*] As previously noted, DDE is a degradation product of the pesticide DDT.

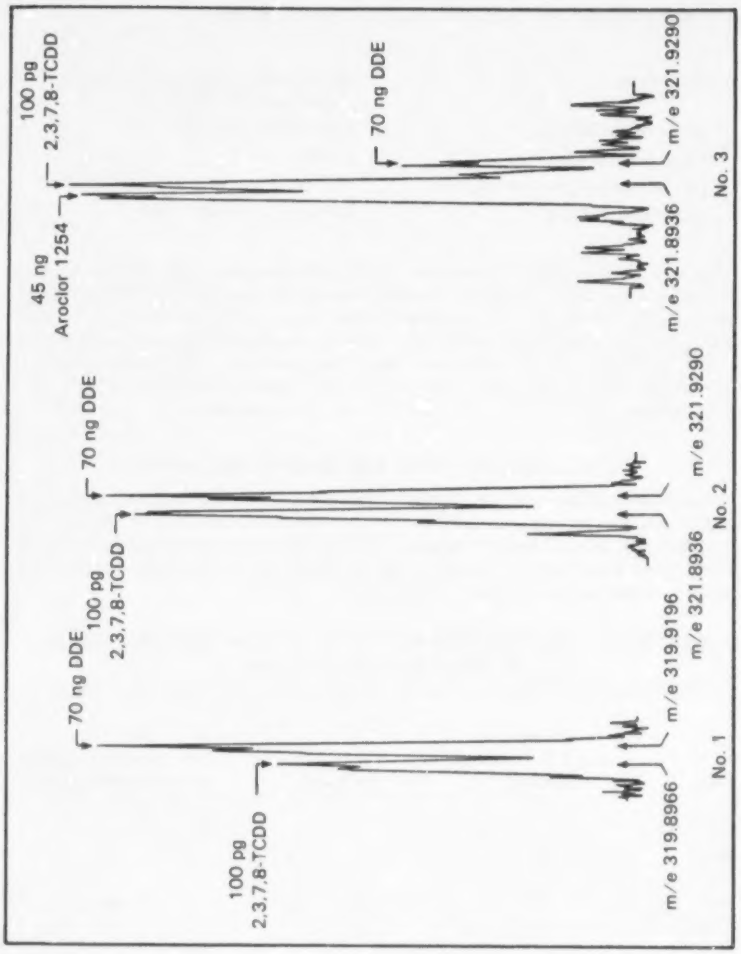


Figure 46. Mass fragmentograms using GC-MS-30 of mixtures of 2,3,7,8-TCDD with other chlorinated compounds.

sample 2 was very high and it was feasible to obtain an actual mass spectral scan as this component of the sample eluted from the gas chromatograph.

Therefore, the MS-30 Mass Spectrometer was set up in the normal magnetic scanning mode, and an aliquot of the extract of sample 2 was injected into the GC. At the appropriate retention time, the mass spectrum of the eluted component was scanned. Before this, we obtained similar mass spectra of a solution containing 10 ng of authentic 2,3,7,8-TCDD standard and of a solvent blank (benzene). The instrumental parameters applicable to the scans are as follows:

Scan rate:	10 sec/decade, beginning 190 sec. after sample injection
Mass range of scan:	m/e 130 to m/e 350
Mass resolution:	1:1000
GC retention time for TCDD:	195 sec.
Other parameters:	Same as described above

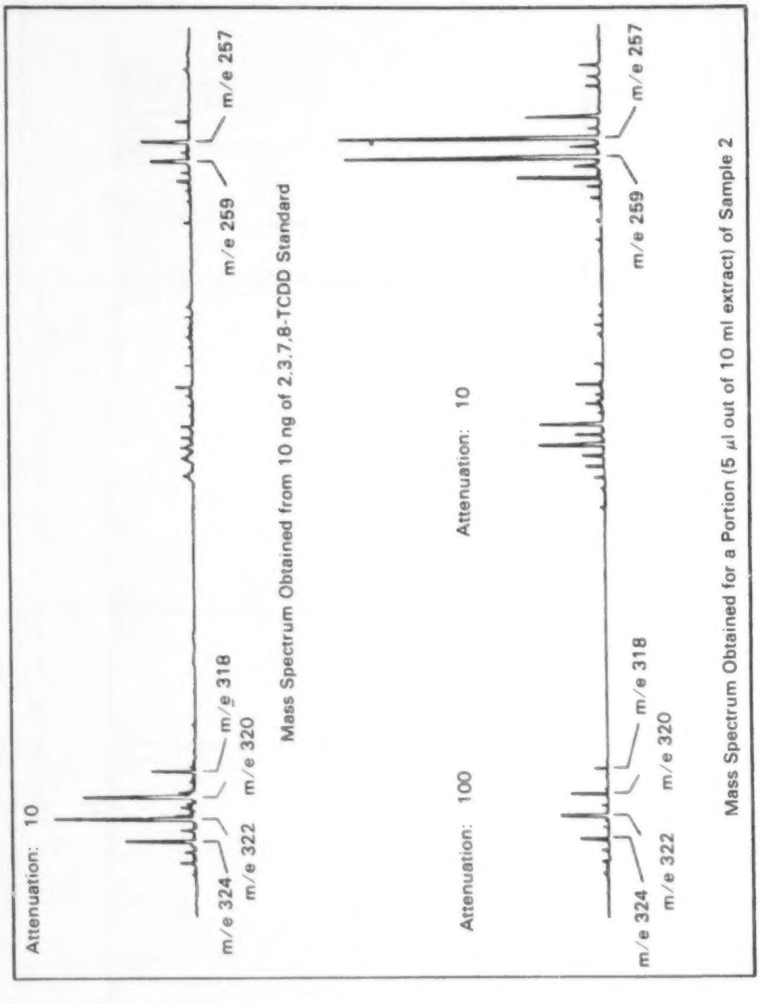
The relative intensities of the more prominent mass spectral peaks recorded in these runs are listed in Table 30. The mass spectra obtained for the 2,3,7,8-TCDD standard and for the extract of sample 2 are shown in Figures 47 and 48. These spectra obviously agree quite well. There is no doubt that the unknown component in sample 2 is a TCDD isomer and that it is present in a high concentration. Apparently some components of the extract of sample 2, other than the TCDD's, also contribute to m/e 194, 257, and 259, but these are not of concern here.

CONCLUSIONS AND RECOMMENDATIONS

As a means of assessing the levels of the extremely toxic TCDD's in process streams, wastes, and sediments from the manufacture of chemicals, a method was developed that proved to be applicable to about 70 percent of the industrial waste sample types examined in this study. These sample types are typical of those that would be collected in a routine chemical plant survey.

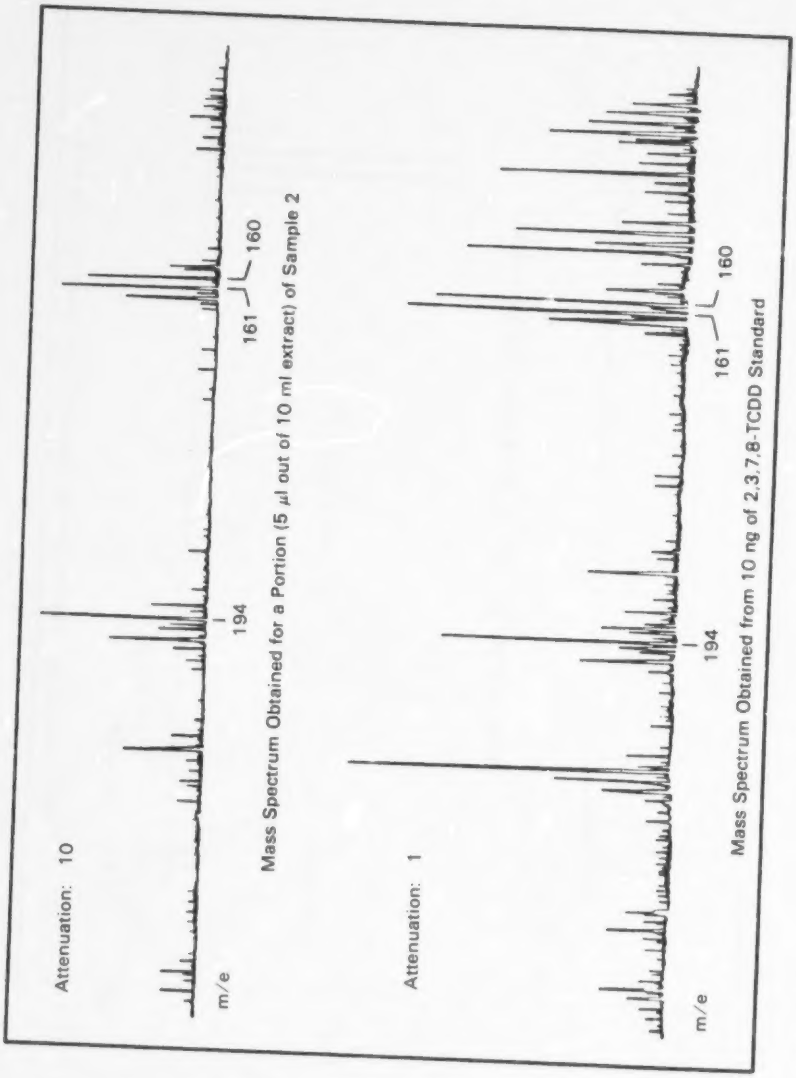
TABLE 30. RELATIVE INTENSITIES OF MAJOR IONS OBSERVED IN MASS SPECTRAL SCANS

m/e	10 ng 2,3,7,8-TCDD standard	Solvent blank	10 μl of EPA sample 2 extract (out of 2000 μl total)
326	10	0	12
324	50	0	48
322	100	0	100
320	80	0	80
318	30	0	25
259	23	0	47
257	34	0	48
194	18	0	30
161	21	4	25
160	17	4	20


Mass Spectrum Obtained from 10 ng of 2,3,7,8-TCDD Standard

Mass Spectrum Obtained for a Portion (5 μl out of 10 ml extract) of Sample 2

Figure 47. Mass spectra from scans of 2,3,7,8-TCDD standard and sample 2 (mass range m/e 330 to m/e 250).



Mass Spectrum Obtained for a Portion (5 µl out of 10 ml extract) of Sample 2

Mass Spectrum Obtained from 10 ng of 2,3,7,8-TCDD Standard

Figure 48. Mass spectra from scans of 2,3,7,8-TCDD standard and sample 2 (mass range m/e 250 to m/e 150).

The analytical methodology implemented in this study is summarized in the following five principal steps:

1. Preparation of a spiked and nonspiked aliquot of each sample in liquid extractable form (organic phase).
2. A sample clean-up procedure that includes acid and base washes to remove the bulk of the sample matrix.
3. An additional sample separation step using liquid chromatography.
4. Screening of samples for detectable levels of TCDD's with a low-resolution GC-QMS system. This step is repeated with a spiked sample if positive levels of TCDD's are detected.
5. Confirmation and quantification of the level of TCDD's by analysis of the samples with a high-resolution GC-MS-30 system.

There are four major advantages with the implementation of this method:

1. The procedure offers a relatively rapid method for qualitative screening of a wide variety of materials for possible contamination by TCDD's, through the use of low-resolution mass spectrometry (GC-QMS showed a MDC of 1 ppb or less in 50 percent of the samples).
2. Only samples in which the initial screening shows TCDD's need be confirmed by use of GC with high-resolution mass spectrometry (minimum resolution 1:10,000).
3. Analysis by high-resolution mass spectrometry yields extremely high sensitivity as well as specificity. The need for both is indicated by the finding of minimum detectable concentrations below 100 ppt in more than half the samples tested.
4. The method warrants a high level of confidence owing to the use of an internal standard and application of the four-ion monitoring technique. Recovery of $^{37}Cl_4$-2,3,7,8-TCDD from spiked samples indicates a recovery range of 40 to 98 percent for the method. Further, by a procedure in which the quantity of native-TCDD's detected is proportionately related to the quantity of $^{37}Cl_4$-2,3,7,8-TCDD added, the data may be automatically corrected for recovery.

Although the procedures outlined here are acceptable for analysis of many industrial process samples, they are not applicable to all sample types. Among those examined in this study, the samples that could not be suitably analyzed are of two types. First are those of biological origin, primarily wood and woodlike products. It is probable that for such samples an acid digestion step is needed to effectively destroy cellular walls and release any residue of TCDD's. Earlier work at Brehm Laboratory on wood and other biological materials confirms the effectiveness of such an approach.

The other type of sample not amenable to the method is more difficult to characterize. Samples of this type formed emulsions in the preparation phase that could not be resolved. Use of several common emulsion-breaking techniques such as addition of excess solvent did not alleviate this problem. Unfortunately, owing to the small number of samples of this type, no further information was obtained. Additional work on such samples would be desirable.

Work should now be conducted toward the development and implementation of the use of capillary columns in identifying each of the individual tetrachloro isomers. This work would require that all of the 22 tetrachlorinated dibenzodioxins be prepared in order to utilize them as standards.

SECTION 5

ROUTES OF HUMAN EXPOSURE

The toxicity of some dioxins, especially 2,3,7,8-TCDD, has been demonstrated in a number of incidents of human exposure. The most serious incidents, including one man-made disaster, have affected the general public; these incidents have resulted from industrial accidents, improper disposition of industrial wastes, and a variety of other exposure routes. In addition to exposures of the general public, human contact with dioxins has occurred in chemical manufacturing plants and in other locations because of the occupational handling of these materials. This report section summarizes both the reported incidents of human exposure to dioxins and the potential exposure routes.

PUBLIC EXPOSURE

Industrial Accidents

The clearest demonstration of dioxin toxicity was a disastrous incident that occurred on July 10, 1976, in Meda, Italy, at a plant producing 2,4,5-TCP for the manufacture of hexachlorophene. The plant was operated by the Industrie Chemiche Meda Societa, Anonima, (ICMESA), an Italian firm owned by the Swiss company Givaudan, which in turn is owned by Hoffman-La Roche, a Swiss pharmaceutical manufacturer. The incident often is described inappropriately as an explosion. A safety disc on an over-pressured 2,4,5-TCP reactor ruptured, and a safety valve opened, releasing the reactor contents directly to the atmosphere (Homberger et al. 1979; Peterson 1978). The quantity of TCDD's released has been estimated to be from 300 g to 130 kg (despite extensive study, there is still no agreement as to the most likely amount) (Bonaccorsi, Fanelli, and Tognoni 1978; Carreri 1978).

The incident occurred late on a Saturday afternoon. It resulted from the closing of a valve that supplied cooling water to the reactor jacket. In the manufacturing process, caustic soda had been used to hydrolyze 1,2,4,5-tetrachlorobenzene in a solvent of ethylene glycol. After the mixture was heated, cooling water was turned onto the jacket and should have remained on until the reaction was complete. A decision had been made to postpone the next operation, a distillation to remove ethylene glycol, until the following Monday. During the standby shutdown procedures the cooling water valve apparently was closed inadvertently. Since the reaction was incomplete, temperature and pressure continued to increase until the limiting pressure of the safety devices was reached. When the release occurred, the regular operators were not in the plant. Five minutes after the release started, someone opened the cooling water valve and the influx of cooling water began to slow down the reaction. Within 15 minutes, release of chemicals to the atmosphere had stopped.

A slight breeze carried the toxic cloud over parts of 11 towns and villages, as condensed chemicals fell from the cloud like snow. The town most affected was Seveso, whose corporate limits adjoin the plant grounds. No emergency action was taken by plant personnel or local authorities, although several people reported to hospitals with chemical burns. Not until the next day, Sunday, was the mayor of Seveso notified of the accident, and officials of other affected towns were not told until Monday. The plant resumed normal operations Monday morning. No official emergency decree was issued until 5 days after the accident, and the possible presence of 2,3,7,8-TCDD was not announced to the local population until after 8 days (Carreri 1978). By then, hundreds of animals had sickened and died, and people with chloracne, principally children, were being hospitalized. Dow Chemical Company has asserted that these deaths probably were due to chlorophenol exposure (Crummett 1980). The plant workers went out on strike, finally closing the plant. Since ICMESA had no suitable laboratory, samples of the contamination had to be sent to Switzerland for analysis; not until 10 days after the accident did Givaudan and Hoffman-LaRoche confirm that the contamination was 2,3,7,8-TCDD. Only then were organized steps taken to assess the damage and to safeguard the health of the people who had been exposed (Reggiani 1977; Peterson 1978; Bonaccorsi, Fanelli, and Tognoni 1978; Carreri 1978).

It was discovered that most of the dioxin had fallen in a narrow strip extending for about 5 km to the southeast from the plant (see Figure 49). The most heavily contaminated area of 267 acres was designated Zone A, and was further divided into seven numbered subzones corresponding to the relative degrees of contamination. The population of Zone A was evacuated. A less contaminated area of 665 acres was designated Zone B; official evacuation of this zone was not ordered. A much larger area was designated Zone R (Respect or Risk), in which dioxin contamination was judged to be too slight to be harmful.

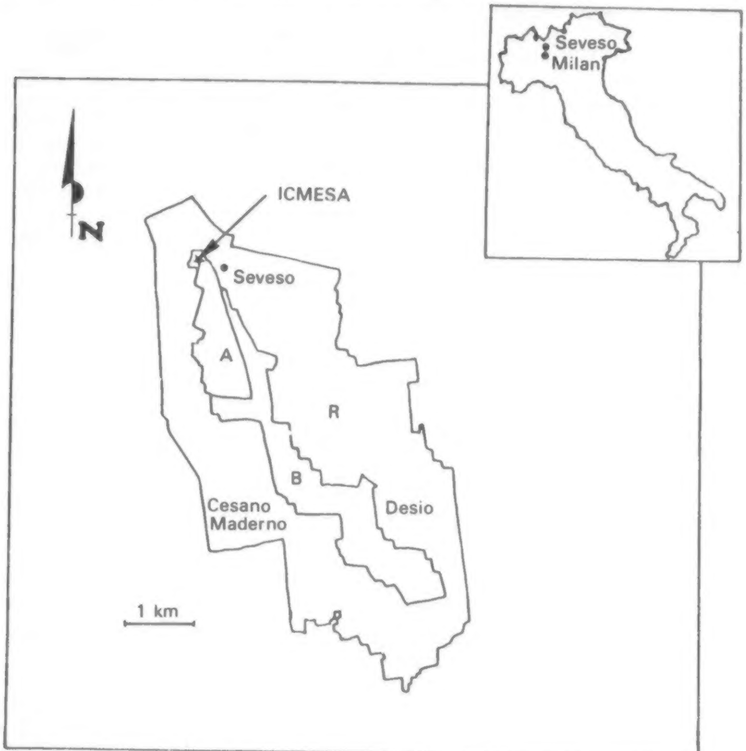


Figure 49. Map of Seveso area showing zones of contamination (A and B) and zone of respect (R).

Source: Adapted from Fanelli et al. 1980.

Chloracne began to appear about 2 days after the accident. Within 6 days, 12 chlidren were hospitalized; within 8 days, there were 14 (Parks 1978). Those first affected were the most seriously affected, and some were still undergoing treatment 3 years after the incident (Revzin 1979). A screening of more than 32,000 children of school age in the Seveso region resulted in the discovery of 187 cases of chloracne (Hay 1978b). Officially, there were 135 confirmed cases within the first year, with "new" waves of the skin disease appearing 18 and 24 months after the accident (Bonaccorsi, Fanelli, and Tognoni 1978). Hoffman-LaRoche reported that most chloracne was of "mild severity and quick recovery" and that there was no increase in the susceptibility of the children to infectious disease (Reggiani 1979a). Only a small percentage of those affected were adults.

Since 2,3,7,8-TCDD had been shown to cause birth defects and spontaneous abortions in laboratory animals, the incidence of birth problems in the affected population was studied. At present, the resulting data are inconclusive and controversial, in part because of poor statistical data from prior years (Toxic Materials News 1979c). Through May 1977, the spontaneous abortion rate for the entire Lombardy region of Italy, which includes the Seveso area, was lower than the worldwide frequency (15 percent versus 20 to 25 percent) (Reggiani 1977). A private organization, however, reported that 146 malformed infants were born during 1978 in the Seveso area, almost 3 times the number reported officially (Chemical Week 1979b; Revzin 1979).

Four years after the ICMESA incident, the people of Seveso are resuming an almost normal life. Hoffman-LaRoche has bought some of the heavily contaminated properties near the plant and has enclosed them and the plant within a tall plastic fence. Contaminated debris and soil from other locations, including the carcasses of 35,000 animals that died or were slaughtered (Parks 1978) have been dumped in the enclosure, and this area is now believed to contain 80 percent of all the dioxin that was released (Chemical Week 1979h). Some nearby houses have been decontaminated by removing the tile roofs, vacuuming and scrubbing the walls with detergents and solvents, and clearing the grounds around them (Parks 1978). All the former residents have been allowed to return to their homes. Having decided the danger is over, many no longer practice any safety precautions (Revzin 1979). None of the many proposals for decontaminating the plant property has satisfied everyone; the situation not only poses a massive technical problem, but is clouded with legal and political difficulties.

The Seveso incident has been called an environmental calamity (Parks 1978), and the release of dioxins has been compared to an escape of nuclear radiation in its potential for disaster (Revzin 1979). The effects of the 20-minute release on July 10, 1976, are still continuing and will not be known for years, perhaps not for generations (Bonaccorsi, Fanelli, and Tognoni 1978). Although no human deaths have resulted from the incident thus far, in the light of present toxicological knowledge, late effects can be expected (Peterson 1978). Operations at the ICMESA plant have not resumed since the 1976 accident (Watkins 1979b).

Contaminated Industrial Wastes

Manufacture of organic chemicals creates wastes, some of which may contain dioxins. In one recorded incident a chemical plant waste known to contain a dioxin has been clearly responsible for illness of a person not associated with chemical handling operations (Beale et al. 1977). Other instances have been recorded and continue to be discovered in which dioxins have been or are being discarded with wastes in a manner that brings them into contact with the general public. This report section lists the known examples of dioxin contamination of public land, air, and water from disposal of industrial wastes. All are associated with present or former producers of 2,4,5-TCP.

Contained or Landfilled Wastes—

The most concentrated waste sources of dioxins are the anhydrous liquids, tars, and slurries, which 2,4,5-TCP manufacturers may discard by burying them in the ground or by storing them in drums. These materials are handled both by personnel of the manufacturing company and by contractors responsible to the manufacturer.

The most notable incident of nonoccupational exposure to dioxin-contaminated wastes of this type involved the spraying of waste oils containing TCDD's on horse arenas and a private road in east-central Missouri in 1971 (Shea and Lindler 1975; Environmental Protection Agency 1975b; Commoner and Scott 1976a; World Health Organization 1977; Kimbrough et al. 1977). The wastes were traced to a plant of the North Eastern Pharmaceutical Co. (NEPACCO) in Verona, Missouri, which manufactured 2,4,5-TCP at that time. The residues of a distillation phase of the process were stored above ground in a 7500-gallon tank. Periodically, NEPACCO would contract with someone to dispose of the wastes. Between February and October of 1971, the Bliss Salvage Oil Company held this contract and during these 8 months hauled away 16,000 gallons. Presumably, most was incinerated. In May and June, however, waste oils mixed with these distillation residues were sprayed to control dusts on four horse arenas and a road on a farm owned by the operator of the oil salvage company.

Unexplained deaths of animals occurred for almost 2 years. By December 1973, over 60 horses had died in the arenas and over 40 had become ill (Commoner and Scott 1976; Kimbrough et al. 1977). Many cats, dogs, rodents, birds, and insects had also died. Seven people developed various disorders as a result of exposure. A six-year-old girl who played regularly on an arena floor was most seriously affected; she was treated for inflammation of the kidneys and hemorrhaging of the bladder, along with other symptoms (Beale et al. 1977). She lost 50 percent of her body weight over the course of the illness, but has since recovered.

Finally, the most heavily contaminated soil was removed from the arenas and replaced. This apparently solved the problem, since no further incidents have been reported. The soil, probably still containing dioxins, is now buried in a landfill and under a concrete highway that was being built at the time (Commoner and Scott 1976a).

In Australia, Union Carbide of Australia Limited (UCAL), previously a manufacturer of 2,4,5-TCP and 2,4,5-T, disposed of dioxin-contaminated wastes by landfilling during the years between 1949 and 1971 (Chemical Week 1978b; Dickson 1978). At the time these wastes were buried, landfilling was the most acceptable method of disposal. It has been estimated that 16 to 30 kg of dioxins may be present in the buried wastes (Chemical Week 1978b; Dickson 1978; Chemical Week 1978c). In 1969, when dioxin contaminants in 2,4,5-trichlorophenol were being publicized, UCAL began removing the dioxins by adsorption onto activated carbon. The dioxin-contaminated carbon, now stored in steel drums, presents a disposal problem (Dickson 1978).

Dioxins have been found in two chemical landfills in Niagara Falls, New York. One of these, the Love Canal, is now the site of a residential community, including a school. The landfill previously was used by the Hooker Chemical Company for burying chemical wastes, including those from the manufacture of 2,4,5-TCP. A rising water table has brought the chemicals to the surface (Chem. and Eng. News 1978). Approximately 80 different chemicals have been identified, including a number of known carcinogens (Cincinnati Enquirer 1978a). Recently it was reported that TCDD's were found at the site (Chemical Week 1979a; Wright State University 1979a, 1979b). About 30 tons of 2,4,5-TCP wastes are buried in the Love Canal. Hyde Park, a larger toxic landfill used by Hooker, also has yielded positive analyses. Environmental evaluations of three plants located near the landfill found TCDD's in dust from these plants and in water samples taken from sediments in a nearby creek (Chemical Regulation Reporter 1980).

One of the largest accumulated quantities of dioxin-contaminated anhydrous wastes now known is a cache of approximately 3000 drums of chemicals found in 1979 at the Vertac plant in Jacksonville, Arkansas (Fadiman 1979). The proper procedure for final disposition of this material, which may contain as much as 40 ppm or more TCDD's, has not been determined. (See Sections 4 and 8 of this report.)

Incinerated Wastes—

A number of present and previous producers of 2,4,5-TCP and 2,4,5-T disposed of wastes by incineration. This method is used by the Dow Chemical Company and was once used by the ICMESA plant and by NEPACCO, which discarded its wastes through a contract incineration company. A recent report has raised a significant question as to whether past or present incineration methods destroy all dioxins. Dow reported in 1978 that fly ash from both stationary tar and rotary kiln incinerators contains low concentrations of dioxins, even that from incinerators designed to burn chemical wastes (Dow Chemical Company 1978). TCDD's bound to particulate matter are largely unaffected by even high-temperature incineration (Rawls 1979; Ciaccio 1979; Miller 1979).

It has been suggested that incineration of dioxin-contaminated chemical wastes is primarily responsible for the observed presence of TCDD's in and around the Dow plant in Midland, Michigan (Merenda 1979; Ciaccio 1979).* If this is shown to be the case, pollution of the atmosphere from chemical incinerators may be an important route in the exposure of the public to dioxin chemicals. Miller (1979) has suggested that a worldwide background of atmospheric dioxin contamination may exist as a result of the incineration by the U.S. Air Force of 10,400 metric tons of Herbicide Orange containing up to 47 ppm TCDD's (see Ackerman et al. 1978). This operation took place in the Pacific in 1977. Although there are no data that confirm the presence of widespread atmospheric pollution from this source, TCDD's were detected in some stack emission samples (Tiernan et al. 1979).

Discharged Water Wastes—

Dioxin concentrations that exceed theoretical solubility limits (Crummett and Stehl 1973) may occur in industrial wastewaters because of 1) the presence of other organic materials in the wastewater that would tend to increase the solubility of the dioxin, and/or 2) the presence of suspended solids to which the dioxins are adsorbed. In either event, it is possible that low levels of dioxins may be carried routinely into the environment by industrial effluents, especially those associated with the production of chlorophenols. Dow has asserted that low levels of dioxins may also be associated with particulate matter leaked to the sewer from scrubbers on powerhouses and incinerators (Crummett 1980).

Little published information addresses the question of dioxins in such industrial water effluents. A 1978 report from Dow Chemical Company contends that their pesticide plant effluent discharges were not responsible for the dioxins found in a number of Tittabawassee River fish, collected downstream from the Dow discharge. The report states that dioxins are formed during any combustion process and therefore may be found everywhere in the environment. In late communications, Dow indicates that dioxins indeed have been found above the Dow effluent outfall by Dr. David Stallings of the U.S. Department of Interior and the Michigan Department of Natural Resources (Crummett 1980).

Other data presented in the Dow report indicate that particulates in scrubber water contained 46 ppb TCDD's, 200 ppb hexa-CDD's, 970 ppb hepta-CDD's, and 120 ppb OCDD. The water was used to scrub the gas stream from a rotary kiln incinerator fired with a supplemental fuel to burn chemical wastes. Disposition of the overflow from the scrubber is unknown; however, it is unlikely that any water treatment system can consistently remove 100 percent of a low-level constituent such as TCDD's, especially if a portion of the TCDD's are adsorbed to particulate matter.

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*Dow believes that the observed presence of TCDD's and other dioxins in Midland and other metropolitan areas is due not only to chemical incinerators but to various other combustion sources such as powerhouses, diesel engines, charcoal grills, etc. (Dow Chemical Company 1978; Rawls 1979).

In 1976, analysis of effluent water from the Vertac plant in Jacksonville, Arkansas, showed 0.2 to 0.6 ppb of TCDD's (Sidwell 1976a). In contrast, analysis of effluent from the city stabilization ponds, to which the plant effluent was sent, showed no TCDD's (Sidwell 1976b). Because no detection limits were reported, the presence of TCDD's in low concentration in the stabilization pond effluent remained a possibility. There was also a question of the validity of the analytical method used in the latter examination.

Chemists at Wright State University have recently reported on the analysis of 100 process and environmental samples taken by the U.S. EPA from the Vertac site and surrounding area (Tiernan et al. 1980). TCDD's were detected in many of the samples at ppt to ppb levels. Composite samples of soil and water from the city sewage treatment plant lagoon contained 8 ppb TCDD's. Bottom core samples from the Vertac cooling pond contained 2 to 102 ppb TCDD's; however, no TCDD's were detected in the cooling pond discharge sample (detection limit of 0.05 ppb). Similarly, liquid discharge samples (2) from the equilization basin contained no detectable TCDD's (detection limit 0.010 ppb), even though a bottom mud sample from the basin contained about 400 ppb TCDD's.

Treatment of wastes at PCP production plants and wood treatment plants is usually accomplished by oxidation ponds, lagoons, or spray irrigation. The efficiency of these treatment schemes has not yet been evaluated where dioxins are concerned. There is evidence, however, that water-mediated evaporation is at least partly responsible for the removal of chlorophenols (and also possibly dioxins) from oxidation ponds (Salkinoja-Salonen 1979b). Insufficient treatment could result in contamination of waterways and thus in potential public exposure.

Transportation Accidents

In January 1979, the derailment of a tank car of orthochlorophenol in Sturgeon, Missouri, resulted in symptoms of chloracne in a cleanup worker. Analysis of the tank car contents showed less than 0.1 percent trichlorophenol contamination and also 37 ppb TCDD's. Subsequent analyses by the EPA confirmed that the dioxin contamination was 2,3,7,8-TCDD (Chemical Week 1979d and 1979e; Poole 1979). Further details of the incident have not been released because of extensive legal actions now pending involving the residents of the town and employees of the manufacturing, transportation, and contract clean-up companies.

Although the incident at Sturgeon is the only one reported in which dioxins were identified, it is especially significant because of the nature of the chemical involved. The manufacture of orthochlorophenol offers no direct chemical pathway to the side reactions that form 2,3,7,8-TCDD. Nevertheless, contamination with this most-toxic dioxin was present. Product distillation is at least a hypothetical origin. Continuing examinations of the source of the 2,3,7,8-TCDD are indicated and are being conducted.

Herbicide Applications

For many years, herbicides made from dioxin-contaminated 2,4,5-TCP were widely distributed into the environment. Since the herbicides were less toxic to grasses, canes, and established trees than to broadleaf weeds and undergrowth plants, they found wide application wherever the objective was to stimulate growth of the more resistant plants. The applications included residential lawns; right-of-ways for power lines, railroads, and highways; forest lands intended for future lumbering; pasturelands; and food crops such as rice and sugar cane. Regulatory and environmental actions have now halted most of these uses of chemicals that may contain dioxins, but a number of public health incidents have been associated with herbicide applications.

In Oregon, application of 2,4,5-T and silvex by timber companies and the government to forest areas has brought charges of increased incidences of miscarriage by women living near the sprayed areas (American Broadcasting Company 1978; WGBH Educational Foundation 1979). It is claimed that among 8 of the women, 11 miscarriages occurred within 1 month after herbicide applications. The EPA investigated these charges and found sufficient evidence of danger of the public health in sprayed areas to place an emergency ban on continued use of 2,4,5-T and silvex in these and other areas (Blum 1979). Other incidents in Oregon involved several people who complained of illness after herbicide sprayings (WGBH 1979). Abortions among cows and deer, and the deaths of fish, quail, and grouse were also reported to be associated with the sprayings (WGBH 1979). An allergist specializing in environmental medicine reported that the complaints of diarrhea and recurrent boils among the exposed people could have been caused by a dioxin contaminant in the herbicides (Anderson 1978).

In northeastern Minnesota, a family reported that offspring of pigs, chickens, and rabbits that had fed in areas sprayed by a U.S. Forest Service helicopter were born deformed, or later developed deformities (ABC News 1978; Anderson 1978; Cincinnati Enquirer 1978c). For over 5 months after the spraying, the family complained of intense bellyaches, headaches, fever, nausea, diarrhea, and convulsions. An analysis of the family's water supply by the Minnesota health authorities revealed traces of a herbicide that contained 2,4-D, and 2,4,5-T. The presence of dioxins was not reported.

Another source of concern is the possible effects of the massive applications of Herbicide Orange in Vietnam. Reports from some researchers indicate that numerous deformities have been found in children 6 to 14 years old (Young et al. 1978). Some reports also state that spontaneous abortions among women in sprayed areas were not uncommon, and that some people died as a result of the spraying. It has been estimated that at least 25,000 children in South Vietnam could be assumed to have acquired hereditary defects from this cause (Young et al. 1978). Others claim that these reports are virtually impossible to validate. The National Academy of Sciences concluded from their studies that there was no consistent correlation between exposure to herbicides and birth defects (Young et al. 1978).

In 1969, citizens of Globe, Arizona, complained of human and animal illnesses after the U.S. Forest Service had applied 3680 pounds of silvex and 120 pounds of 2,4,5-T to the nearby Kellner Canyon and Russell Gulch (Young et al. 1978). After investigation by the Office of Science and Education and by the U.S. Department of Agriculture, it was concluded that there were no significant effects on birds and wildlife, there was no indication of illnesses in livestock greater than in other regions, and human illnesses were those that commonly occur in the normal population, except for one individual who developed skin rash and eye irritation from cleaning out an empty herbicide drum.

In Swedish Lapland, two infants with congenital malformations were born to women who had been exposed to phenoxy herbicides (Young et al. 1978). Medical scientists could find no evidence to substantiate any conclusion beyond a coincidental occurrence of the birth defects and the herbicide spraying.

In New Zealand, two women who had been exposed to 2,4,5-T during their pregnancies gave birth to deformed babies (Young et al. 1978). In one case 2,4,5-T was ruled out as the cause because although the mother had been exposed to the herbicide during pregnancy, the exposure had occurred after the time in the pregnancy when the deformity is known to usually occur. No conclusions were reached on the other case.

Also in New Zealand, it was reported that deformities in infants occurred in three areas of the country and that 2,4,5-T was suspected (Young et al. 1978). After an investigation, it was concluded that there was no evidence to implicate 2,4,5-T as the cause of the deformities.

In Australia, skin rashes, respiratory problems, and higher incidences of birth defects and infant mortality may be associated with 2,4,5-T sprayings and dioxin contaminants (Chemical Week 1978d).

Although no published reports deal with the subject, large segments of the suburban U.S. population are seasonally exposed to 2,4-D spray applications to lawns for weed control. Until 1979, silvex was also a common constituent of many of these formulations.

There is little published information relating to the use of 2,4,5-T in rice fields. Rice is grown in Arkansas, Louisiana, and Texas, and possibly also in Mississippi, usually in localized areas that include facilities for flooding of the fields (a requirement in rice culture). Dioxins, including TCDD's could be accumulating in the soil of these fields or in runoff channels. This appears to be a principal area of missing information with respect to continued use of these herbicides. Dow reportedly has published a study of fish living in rice-field irrigation water that has been treated with 2,4,5-T (Shadoff et al. 1977b).

Foods

A number of human food sources have been found to be contaminated with TCDD's. Three different research teams have reported finding dioxins in the fat of cattle that had grazed on pasture experimentally treated with 2,4,5-T(Meselson, O' Keefe, and Baughman 1978; Kocher et al. 1978; Solch et al. 1978, 1980). Levels reported ranged from 4 to 15 ppt and 12 to 70 ppt, and 10 to 54 ppt, respectively. In contrast, however, samples from cattle fed ronnel contaminated with TCDD's showed no dioxins at a detection limit of 10 ppt (Shadoff 1977). TCDD's have been found at levels ranging from 14 to 1020 ppt in fish and crustaceans collected in South Vietnam (Baughman and Meselson 1973). Fanelli et al. (1980b) and Cocucci et al. (1979) found TCDD's in locally grown garden vegetables, fruit, and dairy milk supplies following the ICMESA accident in Italy in 1976. An investigator analyzed human milk samples collected in 1970 during the herbicide operations in South Vietnam, and found that they were contaminated with 40 to 50 ppt TCDD's (Baughman 1974). He reported that the mothers could have been contaminated either by direct exposure or by ingestion of contaminated foods. About 1 ppt TCDD's has been reported in breast milk from U.S. mothers living near pasture land (Meselson, O'Keefe, and Baughman 1978); however, a subsequent study of 103 samples of breast milk from mothers living in sprayed areas revealed no TCDD's at a detection limit of 1 to 4 ppt (Chemical Regulation Reporter 1980b). In 1973, TCDD's were detected in several U.S. commercial fatty acids (Firestone 1973).

Other chlorinated dioxins have also been detected in foods. Tiernan and Taylor (1978) found hexa-, hepta-, and/or OCDD in 19 of 189 USDA beef fat samples at levels in excess of 0.1 ppb.

Firestone reported finding hexa-CDD's, hepta-CDD's, and OCDD in gelatin samples obtained from supermarkets and in bulk gelatin (Firestone 1977). Gelatin is a byproduct of the leather-tanning industry, which routinely used PCP and TCP as preservatives (U.S. Environmental Protection Agency 1978b). Total United States comsumption of gelatin is estimated at 32 million kilograms per year, of which 20 percent is imported. In this study, dioxins occurred in 14 of 15 commercial gelatin samples at levels ranging from 0.1 to 28 ppb total dioxins. Pentachlorophenol was also identified in most samples. 2,3,7,8-TCDD was not detected in any sample. These data are presented in Table 31.

Analysis by Dow Chemical Company of fish from the Tittabawassee River, which receives the effluent from their Midland complex, revealed the presence of TCDD's, hexa-CDD's, and OCDD in trace quantities (Dow Chemical Company

TABLE 31. DIOXINS IN COMMERCIAL GELATIN[a]

		Dioxins (ppb)[b]								
Sample no.	Sample identity	PCP (ppm)	1,2,4,6,7,9 hexa-CDD's	1,2,3,6,7,9 hexa-CDD's	1,2,3,6,7,8 hexa-CDD's	1,2,3,7,8,9 hexa-CDD's	1,2,3,4,6,7,9 hepta-CDD's	1,2,3,4,6,7,8 hepta-CDD's	OCDD	Total Dioxins
1	Bulk domestic pork skin gelatin	0.0	0.00	0.00	0.00	0.00	0.01	0.00	0.1	0.1
2	Bulk domestic pork skin gelatin	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0	0.0
3	1975 Consumer package (Texas)	3.8	0.00	0.20	0.00	0.03	0.00	0.10	0.2	0.6
4	1975 Consumer package (Texas)	6.4	0.00	0.20	0.00	0.04	0.00	0.30	0.4	1.0
5	1977 Consumer package (Washington, D.C.)	N.A.[c]	0.00	0.00	0.00	0.00	0.02	0.02	0.1	0.2
6	1977 Consumer package (Washington, D.C.)	N.A.	0.03	0.20	0.03	0.05	0.20	0.16	0.2	0.8
7	1977 Consumer package (Washington, D.C.)	N.A.	0.10	0.70	0.40	0.09	0.80	0.80	0.6	3.6
8	Imported bulk gelatin (Columbia, South America)	0.01	0.00	0.00	0.00	0.00	0.20	0.20	0.6	0.9
9	Imported bulk gelatin-A (Mexico)	3.5	0.02,0.03	0.30,0.30	0.40,0.60	0.05,0.02	3.80,3.90	4.60,5.30	20,16	30,26

(continued)

TABLE 31. (continued)

Sample no.	Sample identity	PCP (ppm)	Dioxins (ppb) 1,2,4,6,7,9 hexa-CDD's	1,2,3,6,7,9 hexa-CDD's	1,2,3,6,7,8 hexa-CDD's	1,2,3,7,8,9 hexa-CDD's	1,2,3,4,6,7,9 hepta-CDD's	1,2,3,4,6,7,8 hepta-CDD's	OCDD	Total Dioxins
10	Imported bulk gelatin-A (Mexico)	7.5	0.02,0.02	0.10,0.10	0.30,0.20	0.05,0.09	2.50,2.70	2.80,2.90	20,17	25,23
11	Imported bulk gelatin-A (Mexico)	8.3	0.02,0.02	0.20,0.40	0.60,0.80	0.07,0.20	3.50,4.00	3.60,5.00	21,18	29,28
12	Imported bulk gelatin-B (Mexico)	0.3	0.00,0.00	0.00,0.00	0.00,0.00	0.00,0.00	0.02,0.02	0.02,0.02	0.1,0.1	0.1,0.1
13	Commercial blend (67% domestic pork skin gelatin, 33% Mexican-A)	2.2	0.01,0.01	0.06,0.08	0.20,0.30	0.02,0.09	0.90,0.90	1.20,1.20	4.8,4.3	7.0,6.9
14	Commercial blend (65% domestic pork skin gelatin, 35% Mexican-A)	3.1	0.01,0.01	0.05,0.08	0.10,0.20	0.02,0.07	0.60,0.50	0.80,0.80	2.9,1.9	3.8,3.6
15	Commercial blend (91% domestic pork skin gelatin, 9% Mexican-A)	1.0	0.01,0.01	0.02,0.03	0.04,0.09	0.01,0.02	0.20,0.30	0.30,0.40	1.4,1.1	2.0,2.0

a—Source: Firestone 1977.

b—Limits of quantitation were about 0.006, 0.012, and 0.018 ppb for the hexa-CDD's, hepta-CDD's, and OCDD, respectively, using electron-capture gas-liquid chromatography.

c—N.A. = Not analyzed.

1978). Catfish from the Saginaw Bay contained 0.024 ppb TCDD. Michigan health authorities have found TCDD's in fish from the Flint, Cass, and Shiawassee Rivers. Dow has pointed out that these three rivers have huge combustion sources on their banks but no pesticide plants (Crummett 1980). The Food and Drug Administration has recommended that Michigan set a maximum residue level for dioxins in fish at 100 ppt (Toxic Materials News 1979e).

TCDD's have been recently detected in leather meal, although in unquantified amounts (U.S. Environmental Protection Agency 1978b). Like gelatin, leather meal is a byproduct of the leather-tanning industry. It is reported that the FDA permits up to 1 percent leather meal in swine food diets, but this level is believed to be too restrictive to be economically advantageous. Poultry feeding tests have indicated that 6 percent leather meal in the diet could be economically advantageous if the leather meal were free of dioxins. EPA recently withdrew an application to FDA for approval of the inclusion of leather meal in poultry feed because of the discovery of TCDD's in the meal.

There is no published information relating to the residual level of TCDD's on harvested rice crops that have been treated with the herbicide 2,4,5-T.

Pentachlorophenol has been found in dairy products, grains, cereals, root vegetables, fruits, and sugars (U.S. Environmental Protection Agency 1978e).

Water Supplies

Another apparent gap in information concerns drinking water. There are no published reports of studies that searched specifically for dioxins in surface or well waters used for drinking-water supplies. A report from the National Academy of Sciences (1977) indicates that there are no reports of dioxins in drinking water, but does not indicate clearly whether dioxins have not been detected, or whether no research has been conducted. Dr. James Allen of the University of Wisconsin reported in 1978 that dioxins have been detected in Great Lakes waters, but apparently no data to this effect have been published.

In 1978, Dow Chemical Company reported that their analysts were unable to detect 2,3,7,8-TCDD in two surface water samples taken from the Tittabawassee River near Dow's Midland plant. The detection limit cited was 0.001 ppb.

It is possible that even if toxic chlorodioxins are not present in surface waters, they might be formed at low levels during purification of public water supplies. Early research with unsubstituted dioxins showed that chlorinated dioxins could be formed from the unsubstituted dioxin by direct chlorination (Gilman and Dietrich 1957). Although no tests of this possibility have been reported, any dioxin entering a municipal drinking water system may become chlorinated during routine chlorine disinfection processes, and thus its toxicity could be greatly increased.

Combustion Residues

The presence of dioxins in fly ash from municipal incinerators is described in Section 3. Tests by Dow Chemical Company that found dioxins in fireplace soot and other combustion processes are also described elsewhere in the report. Here it is emphasized that these observations identify another source of exposure of the public to dioxins. To date, the available data are insufficient to allow definition of the relative importance of nonpesticide combustion as a contributor to dioxin pollution of the environment.

Miscellaneous Pesticide Uses

In addition to their principal uses as a raw material and an agricultural pesticide, 2,4,5-TCP and other chlorophenols that may contain dioxins are brought into contact with the public in other ways. One such use is in disinfectants (U.S.

Environmental Protection Agency 1978i). These are used on surfaces of swimming pools, household and hospital sickroom equipment, food processing plants and equipment, and hospital rooms, as well as on surfaces that contact food. They are also used in bathrooms and restrooms, on shower stalls, urinals, floors, and toilet bowls. Another minor use is as a constituent of metal cutting fluids. It is not known whether any of these cutting fluids are sold commercially.

Commercial products containing pentachlorophenol are readily available to the public. Examples of such products are paints containing PCP as a fungicide or preservative, and formulations for wood preserving. The latter typically contain about 4 percent PCP. Exposure of the users of PCP products is most likely to occur during use. In one reported case, however, a woman became weak and lost 20 pounds over a 3-month period that followed the application of paint containing PCP to interior paneling. Chronic inhalation of the PCP vapors from the walls was said to be the cause (U.S. Environmental Protection Agency 1978e).

Dermal absorption of sodium pentachlorophenate (Na-PCP) resulted in the illness of nine newborn infants and the subsequent death of two (U.S. Environmental Protection Agency 1978e). This exposure occurred in a hospital after clothing and linens were accidentally washed with Na-PCP. Analysis of clothing and bed linens showed PCP residues ranging from 2.64 to 195.0 mg/100 g. Analysis for dioxins was not reported.

Since many wood products are treated with PCP, exposure could occur by excessive handling or contact. Items such as telephone posts, fence posts, and similar products, readily accessible to the public, could present health hazards if subsequently handled.

Hexachlorophene Exposures

Until 1972 hexachlorophene was widely used as a bacteriostatic agent in many commercially available products. Hexachlorophene is made from 2,4,5-TCP, a known dioxin source. In September 1972 the FDA began requiring new drug applications for all drugs containing 0.75 percent or more hexachlorophene and also required that these drugs be made available only by prescription. Products containing 0.1 percent hexachlorophene as a preservative are not subject to the prescription requirement and are still marketed commercially.

Hexachlorophene for use in drug and cosmetic products is apparently made from purified 2,4,5-trichlorophenol. The dioxin content of currently marketed hexachlorophene is believed to be less than 15 μg/kg (15 ppb) (World Health Organization 1977). There apparently are no published references that report positive analyses of dioxins in hexachlorophene.

Sickness and death resulting from exposure to hexachlorophene have been reported, occurring primarily among children and infants (Kimbrough 1976; U.S. National Institute of Environmental Health Sciences 1978). It is not known whether dioxin contaminants are responsible. In one incident, four children died following exposure to a detergent containing 3 percent hexachlorophene (Kimbrough 1976). In 1972, 41 infants and children died and a much larger number became ill after being exposed to baby powder to which excessive quantities of hexachlorophene had been added accidentally (Kimbrough 1976). The hexachlorophene concentration in the baby powder was 6 percent.

A Swedish study concerned children born to mothers who were nurses in hospitals and who had been exposed to hexachlorophene soap in early pregnancy; among 65 children, 11 malformations were found, 5 of which were severe (U.S. National Institute of Environmental Health Sciences 1978). Out of 68 children born to unexposed mothers, only one slight malformation was observed.

OCCUPATIONAL EXPOSURE

Except for the 1976 disaster at Seveso, most clearly recognized human injuries associated with dioxins have been suffered by persons who came into contact with the chemicals as a result of their occupation. The most directly affected probably would be workers in plants of the chemical manufacturing industry where the dioxins are created. Other industries and activities, however, also use dioxin-contaminated chemical products and thus represent another source of worker exposure (for purposes of this report, the exposure of Vietnam military personnel to dioxins is considered occupational). Still other occupational exposures result from work in analytical or research laboratories and from handling of chemical wastes. This report section describes the reported incidents and the potential for human exposure due to occupational activities.

A large-scale study of occupational exposure to dioxins is now underway by the National Institute for Occupational Safety and Health (NIOSH). With cooperation from the chemical industry, major unions, and the Department of Defense, NIOSH is compiling a registry of the population of chemical workers in the United States who have had documented exposure to 2,3,7,8-TCDD, either in the manufacture of herbicides or in industrial accidents. Once this registry has been developed, NIOSH plans to evaluate trends in mortality of the exposed workers and, if the data permit, will consider conducting studies of morbidity and reproductive effects (Robbins 1979).

The NIOSH program will augment similar studies in progress in connection with present and former workers exposed to dioxins in Jacksonville, Arkansas, and Nitro, West Virginia (Occupational Safety and Health Reporter 1979).

Chemical Manufacturing Industry

More than 200 dioxin-related industrial accidents occurred around the world during the 30 years prior to 1979 (American Industrial Hygiene Association Journal 1980). The following paragraphs represent only a sampling of these incidents, most of which involve the manufacture of 2,4,5-TCP. Table 32 summarizes some of the other incidents not described in detail. Table 33 is a sampling of the incidents involving plant accidents.

The earliest major incident was an explosion in 1949 at a plant of the Monsanto Company in Nitro, West Virginia. This plant operated from 1948 to 1969, and the explosion was reported to have affected 228 people (Whiteside 1977; Young et al. 1978). The symptoms included melanosis, muscular aches, nervousness, and intolerance to cold, in addition to chloracne. A current occupational study of the long-term effects of dioxin exposure is being conducted of 121 people who were working in the plant at the time, including all of those who developed chloracne as a result of the accident. Preliminary study reports indicate no excess deaths from cancer or cardiovascular disease among these workers (American Industrial Hygiene Association Journal 1980).

In 1953, an explosion occurred in Germany at the factory of Badischer Anilin and Soda-Fabrik, which was producing 2,4,5-TCP by hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of methanol (Goldmann 1972). Following the explosion the safety valves released vapors, which filled all reactor rooms on all four floors of the plant. After a few minutes, vapors that had not been withdrawn with exhause fans had condensed as solids on the apparatus, walls, windows, and doors. Chloracne developed in 42 people, 21 of whom also developed disorders of the central nervous system or internal organs. In addition, 5 years after the explosion a worker replacing a gasket on one of the reactors developed several disorders a few days later; one year later the worker died.

An explosion at the TCP-producing factory of the Coalite and Chemicals Products at Derbyshire, U.K., resulted in 79 workers contracting chloracne (May 1973).

TABLE 32. REPORTED INCIDENTS OF OCCUPATIONAL EXPOSURE TO DIOXINS DURING ROUTINE CHEMICAL MANUFACTURING[a]

Year	Country	Manufacturer/plant location	Chemical produced	Number of persons exposed
1949	West Germany	N.A.[b]/Nordrhein, Westfallen	PCP, TCP	17
1952	West Germany	N.A./N.A.	TCP	60
1952–53	West Germany	Boehringer/N.A.	TCP	37
1954	West Germany	Boehringer, Ingelheim/Hamburg	TCP; 2,4,5-T	31
1956	United States	Diamond Alkali/Newark, NJ	2,4-D; 2,4,5-T	29
1956	United States	Hooker/N.A.[c]	TCP	N.A.
1960	United States	Diamond Shamrock/N.A.[c]	TCP	N.A.
1964	U.S.S.R.	N.A./N.A.	2,4,5-T	128
1964	United States	Dow Chemical Company/Midland, MI	2,4,5-T	60
1965–69	Czechoslovakia	Spolana/N.A.	TCP	78
1970	Japan	N.A./N.A.	PCP; 2,4,5-T	25
1972	U.S.S.R	N.A./N.A.	TCP	1
1973	Austria	Linz Nitrogen Works/N.A.	2,4,5-T	50
1974	West Germany	Bayer/Uerdingen	2,4,5-T	5
1975	United States	Thompson Hayward/Kansas City, MO	TCP	N.A.

a—Adapted from Young et al. 1978.

b—N.A. = Not available.

c—Not known whether occupational exposure was involved in the incident.

TABLE 33. OCCUPATIONAL EXPOSURES TO DIOXINS THROUGH ACCIDENTS IN THE CHEMICAL MANUFACTURING INDUSTRY[a]

Year	Country	Manufacturer/location	Product involved	Number of workers affected
1949	United States	Monsanto/Nitro, WV	TCP	228
1953	West Germany	BSAF/Ludwigshafer	TCP 2,4,5-T	55
1956	France	Rhone Poulene/Grenoble	TCP	17
1962	Italy		TCP	5
1963	Netherlands	Philips-Duphar/Amsterdam	TCP	50
1966	France	Rhone Poulene/Grenoble	TCP	21
1968	United Kingdom	Coalite and Chemicals Products/ Bolsover, Derbyshire	TCP	79
1976	Italy	ICMESA/Meda	TCP	134[b]

a—Adapted from Young et al. 1978.
b—These were not workers but local residents (124 children and 10 adults); no workers were reported affected.

Six months after an explosion in the Netherlands at the Philips-Duphar plant, which was producing 2,4,5-TCP, 9 of 18 men working on decontaminating the plant contracted chloracne (World Health Organization 1977).

During the Seveso incident, the public was more seriously affected, but the plant workers were also exposed to dioxins. Reports are fragmentary and sometimes conflicting. A company-sponsored report says that of the 10 workers in the plant at the time of the accident, none, not even those who came in direct contact with the reactor, showed signs of exposure; further, a year later, none of the plant workers showed any signs of disease associated with dioxin toxicity (Reggiani 1977). Another report states that one volunteer worker, after helping to clean out the material that remained in the reactor after the accident, developed severe chloracne (Parks 1978). Another report states that among 170 workers exposed to the contamination, 12 developed chloracne, 29 developed liver disease, 17 developed high blood pressure, and 20 others suffered from other various disorders (Zedda, Cirla, and Sala 1976). Finally, another report states that 64.5 percent of 141 former workers suffer from liver problems and others suffer from a variety of other complaints; 79 of 160 workers involved in the cleanup campaign show chromosomal abnormalities (Chemical Week 1978a).

Workers at the Vertac plant in Jacksonville, Arkansas may have been affected by exposure to dioxins, even though no catastrophic event occurred during the many years the plant produced 2,4,5-TCP. Graphic accounts of chloracne attacks in plant workers appeared in an investigative article published in a nontechnical U.S. magazine (Fadiman 1979). In June 1979, Arkansas health officials found signs of chloracne in 13 of the 74 current Vertac employees (Richards 1979c). In July 1979, a task force of medical experts began an intensive examination of about 150 present and former employees; no definitive conclusions have been reported.

Although not necessarily employees of chemical manufacturers, some workers undergo occupational exposure to dioxins in the handling or transportation of bulk chemicals outside of the plant. In one reported incident after the railway derailment in Sturgeon, Missouri, low levels of 2,3,7,8-TCDD were found in the blood of two of the cleanup workers (Chemical Week 1979d, 1979e, and 1979i; Poole 1979; Taylor and Tiernan 1979). These were employees of a firm hired by the railroad to clean up the spill.

In a similar incident in Sweden, railroad workers were exposed to 2,4-D and 2,4,5-T. A medical study concluded that these herbicides showed a possible tumor-inducing effect (Young et al. 1978). The presence of dioxins apparently was not considered in this study.

Use of Chemical Products

When makers of dioxin-contaminated products sell these products to other industries or organizations, the personnel of these secondary users are subject to occupational exposure to dioxins. Table 34 lists several related industries that process or handle chemical products with a potential dioxin content.

It is estimated that 80 percent of all pentachlorophenol produced is used in wood-treating operations (Arsenault 1976; American Wood Preservers Institute 1977; U.S. Environmental Protection Agency 1978e). Exposure in this secondary industry may occur during the mixing of the PCP crystals and solvent (American Wood Preservers Institute 1977). Many of the larger wood-treating operations now use automatic closed mixing systems, which limit the chances for worker exposure. Chloracne symptoms have developed, however, in workers in one wood-treating plant; the exposures resulted from manual opening and dumping of bagged PCP (U.S. Dept. HEW 1975). Workers also may be exposed to PCP by handling of wood after treatment.

Other uses for pentachlorophenol and its sodium salt are in cooling tower water treatments, in pulp and paper mills, and in tanneries (U.S. Environmental

TABLE 34. INDUSTRIES USING DIOXIN-RELATED CHEMICALS

Industry	Chemical(s)	Process application
Textiles	TCP	Process water fungicide
Leather tanning	TCP	Process water fungicides
Wood preserving	PCP	Active ingredient in dip vat/ pressure treatment
Pulp and paper	TCP PCP	Process water slimicide, fungicide
Pesticide formulators and applicators	2,4,5-T 2,4-D silvex ronnel erbon hexachlorophene	Active ingredient formulated or sprayed
Automotive	TCP	Metal cutting fluids, foundry core washes
Miscellaneous industries	TCP	Slimicide in cooling tower waters
Household and industrial cleaning products	TCP hexachlorophene	Active ingredient disinfectant
Building/construction	PCP	Termite control
Drug and cosmetics	hexachlorophene	Product preservative or active ingredient
Paint	TCP PCP	Preservative/mildewcide
Farming (cattle)	2,4,5-T 2,4-D	Rangeland weed control
Railroad, telephone (construction and maintenance)	2,4,5-T silvex 2,4-D	Weed control on right-of-ways

Protection Agency 1978e). Potential for worker exposure therefore exists in these industries. Cooling tower waters from one 2,4,5-TCP facility have recently been found to contain ppb levels of TCDD's (see Section 4 of this report).

People involved in the application of herbicides manufactured from or formulated with 2,4,5-TCP and derivatives may be exposed to dioxin contaminants. These include workers involved in aerial applications and those employed by commercial lawn-care companies who apply phenoxy herbicides manually.

Exposures to Herbicide Orange—

Thousands of military personnel were exposed during the Vietnam conflict to Herbicide Orange; these exposures are currently the topic of considerable litigation and are not outlined in detail in this report. The General Accounting Office (GAO) notes that 4800 veterans have asked for treatment for exposure to Herbicide Orange (Toxic Materials News 1979d), and the suits are being brought against former manufacturers, reported to include Dow Chemical Company, Hercules, Diamond Shamrock, Monsanto, Northwest Industries, and North American Philips (Chemical Week 1979c).

Summaries of the situation were published in Science (Holden 1979) and by the New York Times (Severo 1979).

Chemical Laboratories

In 1957, a research worker in a laboratory synthesized 2,3,7,8-tetrabromo dioxin. That same year, another researcher first synthesized 2,3,7,8-TCDD (about 20 grams) by chlorination of unsubstituted dioxin. In both cases, on completion of these achievements, the researcher was hospitalized (Rappe 1978). The chemical laboratory continues to be a potential source of human exposure to dioxins.

One case is reported involving three scientists in the United Kingdom (May 1973). Although it was believed that adequate precautions had been taken, all three were afflicted with various disorders. Two of the scientists had been working on the synthesis of dioxin standards. They had performed the synthesis under a fume hood and had worn overalls and disposable plastic gloves. Both persons developed chloracne in addition to other symptoms. The third scientist, who had been working with dilute dioxin standards, had taken similar protective measures. He did not develop chloracne but he exhibited other symptoms, including hirsutism and excess cholesterol in the blood.

In 1978, Dow Chemical Company reported that an employee contracted chloracne after disposing of laboratory wastes contaminated with dioxins. He reportedly had not followed standard safety procedures. Dow has developed a set of elaborate laboratory safety rules to be used when working with dioxins.

Similarly, stringent procedures are exercised by independent laboratories that analyze samples containing dioxins. The Brehm Laboratory of Wright State University, Dayton, Ohio, includes a specially equipped laboratory with restricted access, specially trained personnel, and tight internal quality control based on mandatory routine wipe tests. All personnel use disposable gowns, gloves, and shoe covers. "Cradle-to-grave" control is exercised for all reagents, wash water, disposable clothing, towels, and all other materials used or consumed in the laboratory; nothing enters the sewer or is discarded as common trash. Everything enters sealable transportation barrels to be discarded in an environmentally acceptable manner. Gas chromatographs are vented through charcoal filter cartridges, which are routinely discarded into the barrels. Any dusty samples are handled in a special filtered glove box with total control of all dust and unused sample material. This laboratory has experienced no incidents of dioxin poisoning (Taylor 1980).

Waste Handling

Another possible route of exposure to workers is the handling of production wastes generated from manufacturing and formulation processes. Not only the employees of the company that generates dioxin-containing wastes can be affected by these wastes, but also those who work for contract waste disposal firms. The incident at Verona, Missouri, indicates that the waste disposal company owner and /or his employees did not recognize the dangers of wastes with potential dioxin content.

The synthesis of pentachlorophenol and its use in wood treatment also generate waste products. A current study sponsored by the EPA Office of Solid Wastes includes an analysis of sludge samples from various locations within three industrial plants that produce either trichlorophenol, pentachlorophenol, or hexachlorophene (U.S. Environmental Protection Agency 1978d). Also being sampled is a wood-preservation operation in which pentachlorophenol is used. Initial results have shown low-ppm concentrations of hexa-CDD's, hepta-CDD's, and OCDD in sludges resulting from PCP production. Concentrations of the dioxins are not specified, but it is stated that the levels are below those designated as toxic in the published literature. Also, 0.06 ppm OCDD and low levels (not quantified) of hexa-CDD's and hepta-CDD's were found in the soil in the vicinity of the product storage area.

SECTION 6

HEALTH EFFECTS

INTRODUCTION

On a molecular basis 2,3,7,8-TCDD is perhaps the most poisonous synthetic chemical. As shown in Table 35, only bacterial exotoxins are more potent poisons. Not only is this TCDD isomer extremely poisonous but it also has extremely high potential for producing adverse effects under conditions of chronic exposure. Human exposure to 2,3,7,8-TCDD has induced chloracne (an often disfiguring and persistent dermatologic disorder), polyneuropathy (multiple lesions of peripheral nerves), nystagmus (involuntary rapid movement of the eyeball), and liver dysfunction as manifested by hepatomegaly (increase in liver size) and enzyme elevations (Pocchiari, Silano, and Zampieri 1979). In animals, this compound has been shown to be teratogenic, embryotoxic, carcinogenic, and cocarcinogenic (Neubert and Dillman 1972; Courtney 1976; Kociba et al. 1978; and Kouri et al. 1978). It has been established that under certain conditions 2,3,7,8-TCDD can enter the human body from a 2,4,5-T-treated food chain and can accumulate in the fatty tissues and secretions, including milk (Galston 1979). The available data indicate significant risks associated with the use of dioxin-contaminated herbicides. Based upon the work of Van Miller et al., estimates done by accepted risk assessment procedures indicate that daily human exposure to 0.01 μg (10 ng) of 2,3,7,8-TCDD is the dosage expected to result in "incipient carcinogenicity." Additionally, daily human exposure to 4 μg 2,3,7,8-TCDD would be expected to result in a shortened lifespan, and daily exposure to 290 μg would likely result in acute toxicity (Galston 1979).

Although 2,3,7,8-TCDD is considered to be the most toxic dioxin, others are also cause for concern. Kende and Wade (1973) have established certain chemical structural requirements that must be met for a dioxin to be toxic:

- Halogen substituents at positions 2, 3, and 7 are minimum structural requirements.
- Bromine as a substituent is more active toxicologically than chlorine, which is more active than fluorine.
- At least one hydrogen atom must remain on the dibenzo-*p*-dioxin nucleus.

Another finding is that the ability for a dioxin to induce* various enzymes correlates with its toxicity, as illustrated in Tables 36 and 37. As these tables show, 2,3,7,8-TBDD and Hexa-CDD are the only dibenzo-*p*-dioxin derivatives nearly comparable to 2,3,7,8-TCDD in acute toxicity or ability to produce chloracne. These two compounds are also comparable to 2,3,7,8-TCDD in induction of aryl hydrocarbon hydroxylase (AHH). The compounds OCDD and 2,7-DCDD are mildly toxic, with minimal ability to induce AHH. Thus bioassays of unknown dioxin isomers based upon enzyme induction hold promise for predicting biological activity and toxicity.

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*An induced enzyme is one that is synthesized only in response to the presence of a certain substrate or substrates.

METABOLISM

In guinea pigs, 2,3,7,8-TCDD is moderately well absorbed from the gastrointestinal tract and has a plasma half-life of about 1 month (Nolan et al. 1979). Although dibenzo-*p*-dioxin is rapidly converted by the microsome-NADPH system into polar metabolites, this system has little effect upon 2,3,7,8-TCDD (Vinopal and Casida 1973). A large proportion of administered 2,3,7,8-TCDD persists in unmetabolized form in the liver, partially concentrated in the microsomal fraction in all species studied. This finding implies that the unmetabolized compound, rather than a metabolite, is responsible for its toxic effects in mammals. A recent study has shown that 2,3,7,8-TCDD is slowly excreted via the biliary tract in the form of glucuronide and other more polar metabolites (Ramsey 1979). The same study indicated that enterohepatic recirculation of the compound was not extensive. Studies have indicated that its toxicity is not mediated by:

- Inhibition of mitosis (cell division) in mammalian cells
- Alteration of glucocorticoid metabolism
- Alteration of thyroid hormone function

TABLE 35. TOXICITIES OF SELECTED POISONS[a]

Substance	Molecular weight	Minimum lethal dose (moles/kg)
Botulinum toxin A	9.0×10^{5}	3.3×10^{-17}
Tetanus toxin	1.0×10^{5}	1.0×10^{-15}
Diphtheria toxin	7.2×10^{4}	4.2×10^{-12}
2,3,7,8-TCDD[b]	322	3.1×10^{-9}
Saxitoxin	372	2.4×10^{-8}
Tetrodotoxin	319	2.5×10^{-8}
Bufotoxin[c]	757	5.2×10^{-7}
Curare	696	7.2×10^{-7}
Strychnine	334	1.5×10^{-6}
Muscarin[c]	210	5.2×10^{-6}
Diisopropylfluorophosphate	184	1.6×10^{-5}
Sodium cyanide	49	2.0×10^{-4}

a—Source: Poland and Kende 1976. These data were compiled by Mosher et al., and the values indicate only relative toxicity. It should be noted that the values deal with different species, routes of administration, survival times, and in one case the mean lethal dose rather than the minimum lethal dose. Except where noted, administration was by the intraperitoneal route in mice.

b—LD_{50} upon oral administration in the guinea pig.

c—Intravenous injection in the cat.

TABLE 36. BIOLOGICAL PROPERTIES OF DIOXINS[a]

Compounds	LD_{50} (rat) (mg/kg)	Chloracne aptitude	Teratogenic effect	Embryotoxic effect
2,3,7,8-TCDD	0.04	+++	+++	+++
Unsubstituted dioxin	>1000	o	o	o
2,7-DCDD	∿2000	o	±	±
2,3-DCDD	>1000	o	o	o
2,3,7-tri-CDD	>1000			
2,3,7-tri-BDD	>1000			
1,2,3,4-TCDD	>1000	o	o	o
1,3,6,8-TCDD	> 100	o	o	o
2,3,7,8-TBDD	≤ 1	+++		
Hexa-CDD (mixture)	∿ 100	+	++	++
OCDD	∿2000	o	±	+

a—Source: Saint-Ruf 1978. Values for symbols were not reported.

- Increasing serum levels of ammonia
- Inhibition of the synthesis of flavin enzymes or
- The effect of superoxide anion via DT-diaphorase stimulation (Beatty 1977).

Another aspect of 2,3,7,8-TCDD metabolism is its interaction with iron metabolism. Rats given 1.7 μg of the substance intragastrically have shown a 2-fold increase in the serosal transfer of iron, whereas no effect was observed on the mucosal iron uptake (Manis 1977). Sweeny (1979) has shown, however, that iron deficiency protects mice from many of the toxic effects of 2,3,7,8-TCDD. In the latter study, animals rendered iron-deficient were protected from elevated porphyrin levels (including the consequent skin disease that resembles human porphyria cutanea tarda) and liver damage. Since mixed function oxidase enzymes were elevated in the iron-deficient mice, the authors speculated that depleted stores of iron in tissue were responsible for the observed amelioration of toxicity. The results of these studies have significant implications for toxicity in humans. Persons with high dietary iron intake would be expected to be more susceptible to 2,3,7,8-TCDD toxicity than persons with marginal iron intakes. Similarly, females might be less susceptible to its toxicity than males because they usually store less iron in the body.

Pharmacokinetics and Tissue Distribution

Two studies have extensively examined the pharmacokinetics of 2,3,7,8-TCDD (Piper, Rose, and Gehring 1973; Rose et al. 1976). Rose demonstrated that elimination of this dioxin followed first-order kinetics, and he fit the data to the one-compartment open model. Table 38 shows the body burden of ^{14}C-2,3,7,8-TCDD in rats given a single oral dose of 1.0 μg/kg; the average fractional oral absorption of ^{14}C-2,3,7,8-TCDD was approximately 84 percent, and the elimination half-life averaged 31 days. Piper's earlier study also found that after the first 2 days following oral dosages of rats, elimination followed first-order kinetics. The results of this study, however, which are summarized in Figure 50, show that only about 70 percent of ingested 2,3,7,8-TCDD was absorbed and the elimination half-life was only about 17 days. Over a 21-day period, a total of 53 percent of the ingested dose was excreted in the feces, while about 13 percent and 3 percent were excreted in the urine and expired air, respectively.

Tissue distribution of ingested 2,3,7,8-TCDD has been examined in many species, including rats, guinea pigs, and monkeys (Piper, Rose, and Gehring 1973; Rose et al. 1976; Gasiewicz and Neal 1978; Van Miller, Marlar, and Allen 1976). Rose et al. established that the accumulation of ^{14}C-2,3,7,8-TCDD in rat liver follows apparent first-order kinetics. In this study, the accumulation of 2,3,7,8-TCDD in rat liver could be simulated by the following equation:

$$C_t = C_{ss}(1 - e^{-kt})$$

where C_t = the concentration of ^{14}C activity in the liver at time t
C_{ss} = the concentration of ^{14}C activity in the liver at steady state
K = elimination rate constant from the liver

TABLE 37. ENZYME INDUCTION[a]

Compounds	ALAS[b] (chick embryo)	AHH[c] (chick embryo)	Zoxazolamine hydroxylase (rat)
2,3,7,8-TCDD	+++	1.00	+++
Unsubstituted dioxin			o
2,3-DCDD	o	0.00	
2,7-DCDD	o	0.00	
2,8-DCDD	o	0.00	
1,3-DCDD	o	0.00	
2,3,7-tri-CDD	++	0.02	
2,3,7-tri-BDD	++	0.60	
1,2,3,4-TCDD	o	0.00	
1,3,6,8-TCDD	+	0.20	
2,3,7,8-TBDD		1.00	+++
Hexa-CDD		0.80	
OCDD		0.00	o

a—Source: Saint-Ruf 1978. Values for symbols not reported.
b—Amino-levulinic Acid Synthetase.
c—Aryl Hydrocarbon Hydroxylase.

TABLE 38. ^{14}C BODY BURDEN ACTIVITY IN SIX RATS GIVEN A SINGLE ORAL DOSE OF 1.0 μg OF ^{14}C-2,3,7,8-TCDD/kg[a]

Sex	f	k (days^{-1})	$t_{1/2}$ (days)
Male	0.66	0.026 ±0.001[b]	27
Male	0.77	0.018 ±0.001	39
Male	0.91	0.021 ±0.000	33
Female	0.93	0.022 ±0.001	32
Female	0.87	0.019 ±0.001	36
Female	0.91	0.033 ±0.002	21
Mean ±SD	0.84 ±0.11	0.023 ±0.006	31 ±6

a—Source: Rose et al. 1976. Rose gives the following equation:

$$\text{Body burden} = f\,(\text{dose})e^{-kt}$$

where f is the fraction of the dose absorbed; k, the elimination rate constant; $t_{1/2}$, the body burden half-life.

b—Confidence limits 95%.

Values of C_{ss} equal to 0.25 μg equivalent 2,3,7,8-TCDD per gram of liver per μg dose, and k equal to 0.026 days^{-1} were obtained by fitting experimental data. In this study, the concentration of the dioxin in rat liver was 5 times greater than that in fat, while concentrations in kidney, thymus, and spleen were 1/12th to 1/50th of those in the liver. Rose et al. (1976) also assumed that first-order elimination kinetics applied to accumulation of 2,3,7,8-TCDD in rat fat, and they calculated values of C_{ss} and k equal to 0.058 μg equivalent TCDD per gram of fat per μg dose and 0.029 day^{-1}, respectively. Additional clearance and accumulation data were published by Fries and Marrow in 1975.

In a study of male guinea pigs, Gasiewicz and Neal (1978) found the highest levels of radioactivity (percent of original dose per gram of tissue) on day 1 after injection in the adipose tissue (2.36 percent), adrenals (1.36 percent), liver (1.13 percent), spleen (0.70 percent), intestine (0.92 percent), and skin (0.48 percent). On day 15 of this study, the level of ^{14}C-2,3,7,8-TCDD in the liver had increased to 3.23 percent/g; increases were also noted in the adrenals, kidneys, and lungs, and general decreases were seen only in adipose tissues and skin.

Van Miller et al. (1975) found that 40 percent of the radioactivity of an administered dose of labeled 2,3,7,8-TCDD was concentrated in rat liver, whereas less than 10 percent was concentrated in monkey livers. In this study, high concentrations of the radioactivity were found in the skin, muscle, and fat of monkeys. Thus, there appear to be significant differences in the tissue distribution of 2,3,7,8-TCDD among various animal species.

One study examined the tissue distribution and excretion of labeled OCDD in the rat (Norback 1975). A radioactive analog of OCDD at a daily dosage of about 12.4 mg/kg was administered for 21 days. Over 90 percent of the OCDD administered was recovered in the feces as unabsorbed material. The major route of elimination of absorbed OCDD in the rat was the urinary system, and the rate corresponded to a biological half-life of about 3 weeks. After 21 days of administration, approximately 50 percent of the body burden of OCDD was found in the liver; over 95 percent of the radioactivity in the liver was associated with the microsomes and was equally distributed within the rough and smooth fractions. The radioactivity in adipose tissue was about 25 percent of that in the liver. Significant levels of radioactivity were also found in the kidneys, breast, testes, skeletal muscle, skin, and serum.

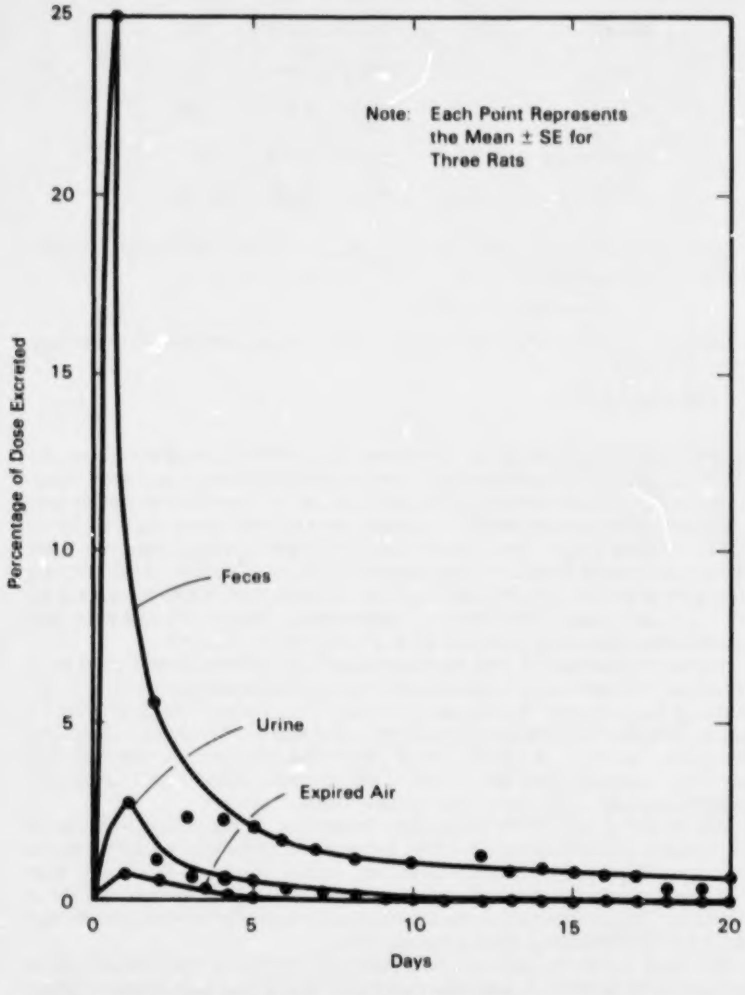

Figure 50. Excretion of ^{14}C activity by rats following a single oral dose of 50 μg/kg (0.14 μCi/kg) 2,3,7,8-TCDD.

Source: Piper, Rose and Gehring 1973.

Enzyme Effects

Several investigations show that 2,3,7,8-TCDD has a dramatic influence upon various enzyme systems in many species including man. The most notable were the mixed-function oxygenases. For example, 2,3,7,8-TCDD is approximately 30,000 times more potent than 3-methylcholanthrene in inducing activity of the enzyme aryl hydrocarbon hydroxylase (AHH) in rat liver (Poland and Glover 1974). This dioxin is also a potent inducer of δ-amino-levulinic acid synthetase in the liver of chick embryo (Poland 1973). These properties of 2,3,7,8-TCDD have a considerable influence upon its toxicity. For instance, its ability to act as a cocarcinogen or to produce porphyria cutanea tarda depends upon alteration of enzymatic systems. Before the effects on enzymatic systems are catalogued, an examination of the mechanism of its effects on the cytochrome P-450-mediated monooxygenase enzyme system may prove informative. This enzyme system handles much of the influx of "foreign" chemicals and appears to rival the immune system in complexity (Fox 1979).

A well-characterized subset of the P-450-mediated enzymes is a group of cytochromes whose induction is regulated by one of a small number of genes. Fox (1979) has termed this genetic system the Ah complex (for aromatic hydrocarbon responsiveness). Work with 2,3,7,8-TCDD has demonstrated that the Ah locus must involve a minimum of three gene products at each of two nonlinked loci, plus a structural gene for cytochrome P_1-450 (P-448) as well. Other investigators have demonstrated that cytosolic binding sites for 2,3,7,8-TCDD enhance AHH activity by de novo* protein synthesis of apocytochrome P-448, and that these binding sites are not necessarily associated with AHH inducibility regulated by the Ah locus (Guenthner and Nebert 1977; Kitchin and Woods 1978). It has been postulated that the rate-limiting factor in AHH induction is protein synthesis of apocytochrome P-448 (Kitchin and Woods 1978). Fox (1979) suggests that 2,3,7,8-TCDD may act in a manner similar to steroid hormones. He postulates that the dioxin may ride its receptor into a cell's nucleus, where it turns on specific Ah genes. Activation of these genes would then lead to the requisite protein synthesis for AHH induction.

Figure 51 summarizes the mechanism of AHH induction proposed for 2,3,7,8-TCDD and possibly the mechanism by which this substance produces other toxic effects. As the figure shows, 2,3,7,8-TCDD moves into a cell and binds to a specific cytosolic receptor. The receptor-dioxin complex then moves into a cell's nucleus, where it "turns on" the synthesis of specific messenger RNAs, which direct the synthesis of cytochrome P_1-450. Other 2,3,7,8-TCDD molecules can then react with newly formed cytochrome P_1-450, possibly to produce reactive intermediates. These metabolites may be excreted as innocuous products, may afflict specific critical target cells in other organs, or may act as carcinogens or cocarcinogens.

Several studies show that 2,3,7,8-TCDD induces many enzyme systems and suppresses others. Studies with rats indicate that females are more susceptible than males to enzyme alteration by the dioxin (Lucier et al. 1973). Further, 2,3,7,8-TCDD induces the following enzymes in addition to AHH, δ-amino-levulinic acid synthetase, and the cytochrome P-450-containing monooxygenases, mentioned earlier:

- UDP glucuronyl transferase (Lucier 1975);
- Aldehyde dehydrogenase (Roper 1976);
- Glutathione transferase B (Kirsch 1975);
- DT-diaphorase (Beatty and Neal 1976);
- Benzopyrene hydroxylase (Lucier 1979);

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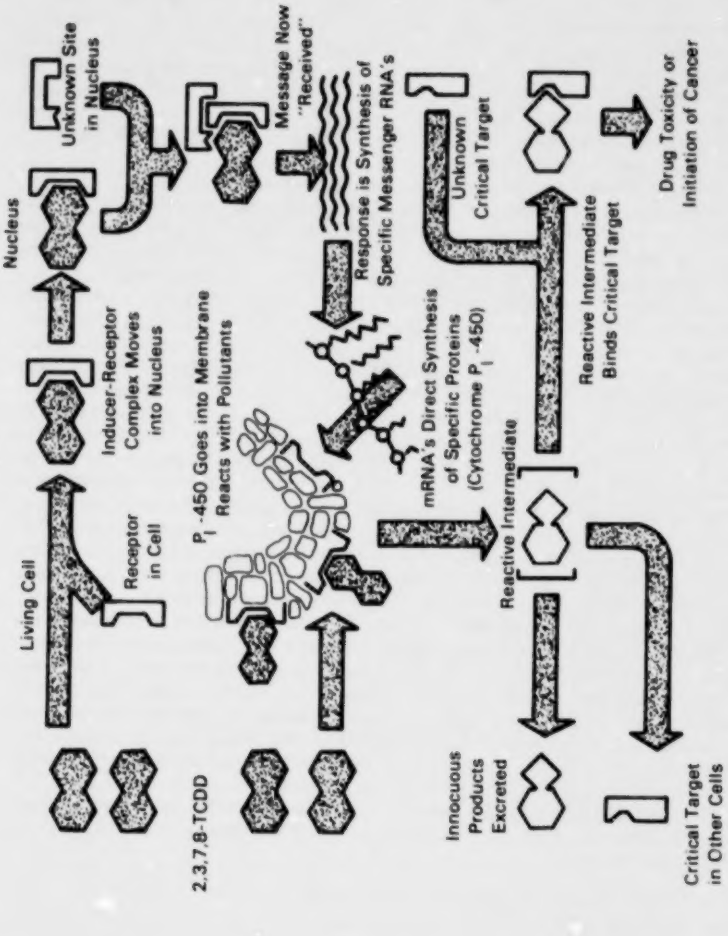
*primary or of recent onset



2,3,7,8-TCDD
Living Cell
Receptor in Cell
Inducer-Receptor Complex Moves into Nucleus
Nucleus
Unknown Site in Nucleus
P_I-450 Goes into Membrane Reacts with Pollutants
mRNA's Direct Synthesis of Specific Proteins (Cytochrome P_I-450)
Response is Synthesis of Specific Messenger RNA's
Message Now "Received"
Innocuous Products Excreted
Reactive Intermediate
Reactive Intermediate Binds Critical Target
Unknown Critical Target
Critical Target in Other Cells
Drug Toxicity or Initiation of Cancer

Figure 51. Proposed mechanism for induction of AHH and toxicity by 2,3,7,8-TCDD (adapted from Fox 1979).

- Glutathione S-transferase (Manis 1979);
- Ethoxycoumarin deethylase (Parkki and Aitio 1978).

Marselos et al. (1978) found that 2,3,7,8-TCDD decreases activity of the following enzymes:

- UDP-glucuronic acid pyrophosphatase;
- D-glucuronolactone dehydrogenase;
- L-gluconate dehydrogenase.

The following enzymes have shown no effects upon exposure to 2,3,7,8-TCDD:

- NADPH cytochrome (Lucier et al. 1973);
- B-glucuronidase (Lucier et al. 1973);
- UDP-glucose dehydrogenase (Marselos et al. 1978);
- Epoxide hydrase (Parkki and Aitio 1978);
- Glycine N-acetyl transferase (Parkki and Aitio 1978).

As these lists indicate, the effects of 2,3,7,8-TCDD on more than a dozen enzyme systems have been studied extensively.

Effects on Lipids

2,3,7,8-TCDD has dramatically altered the lipid profiles in laboratory animals and man. One study examined the effects of both sublethal and lethal doses upon the lipid metabolism of the Fischer rat (Albro 1978). A sublethal dose of 2,3,7,8-TCDD caused a temporary increase in triglyceride and free fatty acid levels, with a persistent decrease in levels of sterol esters. Lethal doses resulted in fatty livers and large increases in serum cholesterol esters and free fatty acids, with little change in triglyceride levels. These changes appeared to be due in part to damage sustained by lysosomes. A decrease in acid lipase activity observed in the study also supports the hypothesis that the 2,3,7,8-TCDD-induced myeloid bodies (see Figure 52) were derived from damaged lysosomes and probably accounted for the increased levels of cholesterol esters in animal livers. A mechanism by which 2,3,7,8-TCDD may exert its toxic effects is suggested by the observed rapid, dose-dependent increase in lipofuscin pigments.* Lipid peroxidation, which precedes the formation of polymeric lipofuscins, is known to seriously damage membranous subcellular organelles, including lysosomes.

Studies of workers occupationally exposed to 2,3,7,8-TCDD have shown lipid abnormalities (Walker and Martin 1979; Poland et al. 1971). In Poland's study, 7 of 71 persons (10 percent) occupationally exposed to the dioxin in a plant manufacturing 2,4-D and 2,4,5-T showed elevated serum cholesterol levels (greater than 294 mg/100 ml). Walker's more recent study of eight dioxin-exposed workers with chloracne showed significant abnormalities in lipid metabolism and liver function. In this study, the levels of triglycerides and γ-glutamyl transpeptidase (GGT)** were elevated in five men and were normal in the other three. In all of the dioxin-exposed workers with chloracne, however, the levels of high-density lipoprotein (HDL) cholesterol were below the method mean, total cholesterol levels were above the method mean, and ratios of total to HDL cholesterol were consistent with a higher-than-average risk of ischemic (oxygen insufficiency) vascular disease. Two of the men in the study had experienced previous myocardial infarction (heart attack), and one had experienced possible transient ischemic attacks (TIA's) (reversible cerebrovascular insufficiency). In any event, the lipid abnormalities resulting from 2,3,7,8-TCDD exposure may be a significant risk factor for ischemic vascular disease.

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*Bronze-colored (wear-and-tear) pigments.

**Liver enzyme.

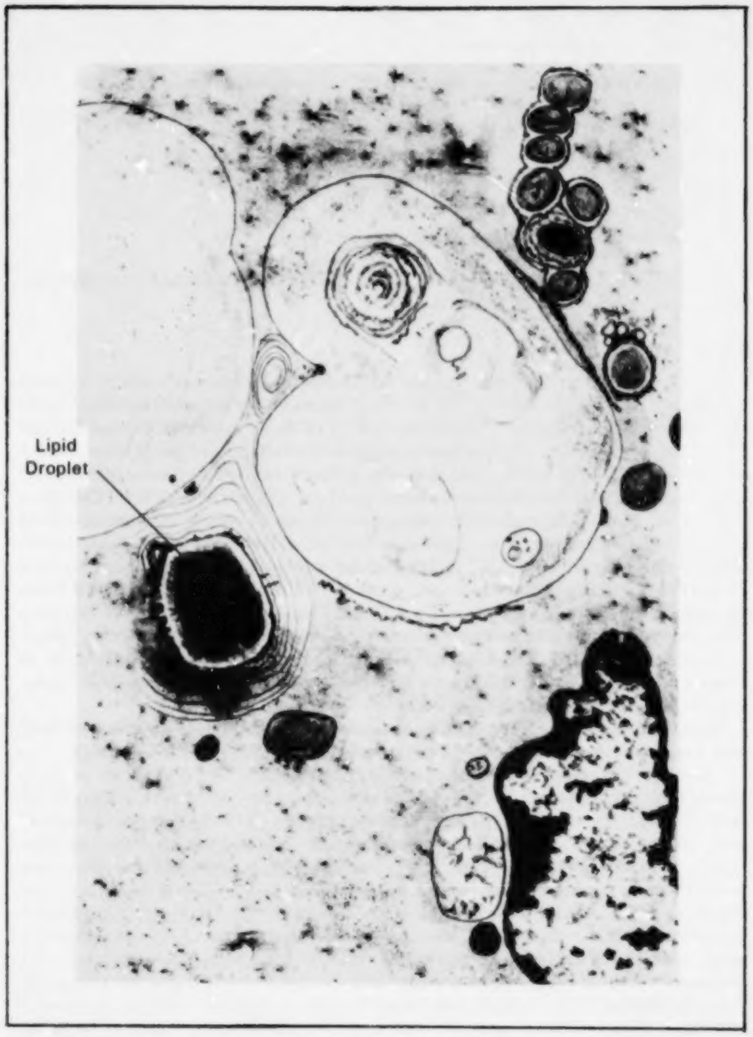

Figure 52. Schematic of rat liver 13 days after administration of 2,3,7,8-TCDD (50 µg/kg). Note concentric membrane array surrounding lipid droplet. X20502.

Source: Redrawn from Albro 1978.

GROSS AND HISTOPATHOLOGIES

The gross (macroscopic) and histopathologies (microscopic) of dioxin-exposed chickens, rats, and monkeys have been examined extensively (Gupta et al. 1973; Norback and Allen 1973; Allen 1967; Allen et al. 1975; Greig and Osborne 1978). The chicken develops extreme morbidity and mortality at dietary concentrations of 2,3,7,8-TCDD that are only mildly toxic to rats, whereas response in the monkey is intermediate (Norback and Allen 1973). At postmortem examination, the most striking finding in dioxin-exposed animals is usually substantial loss of body fat.

Two types of lesions have been reported in all species studied: (1) involution of the thymus; and (2) testicular alterations, including atrophy, necrosis, and abnormal spermatocyte development. One lesion, hypertrophic gastritis, has been observed only in primates. This lesion is characterized by marked hypertrophy of the gastric (stomach) mucosa, which occurs in the fundic and pyloric regions combined with small gastric ulcers penetrating the mucosa (Allen 1967).

In experiments with *Macaca mulatta* monkeys exposed to dioxins (Allen 1967; Allen et al. 1975; Norback and Allen 1973), researchers found reduced hematopoiesis (formation of blood cells) and spermatogenesis, degeneration of the blood vessels, focal necrosis of the liver, and gastric ulcers. Under gross observation, experimental monkeys exhibited obvious dilatation of the heart, especially on the right side. Under microscopic examination, the cardiac muscle fibers were distinctly separated by fluid, and individual muscle cells were hypertrophic, with enlarged, distorted, and hyperchromic nuclei (see Figures 53 and 54). Although the lungs of the animals were not altered appreciably, isolated areas of atelectasis (small areas of collapse), congestion, edema, and fibrosis were observed. Livers from the monkeys were small, firm, and moderately yellow, with many enlarged, multinucleated parenchymal cells. Necrosis of parenchymal liver cells occurred in the centrilobular zone, and some areas of fibrosis occurred in the periportal area. Spleens from the animals were small; the germinal centers were surrounded by only scattered lymphocytes, and the blood sinuses were practically devoid of cells. The seminiferous tubules of the testes had abundant spermatogonia and sertoli cells; only a few primary spermatocytes were present, however, and no spermatids or mature spermatozoa were observed. Gastrointestinal changes have been described earlier.

Mesenteric (abdominal) lymph nodes of the monkeys were light tan and edematous, microscopically resembling the splenic disarray of cellular architecture. Grossly, the bone marrow resembled coagulated plasma. Microscopically, only a few hematopoietic cells were seen in the marrow; these were equally divided between members of the myeloid (white blood cell line) and erythroid (red blood cell line) series. Changes in the skeletal muscle resembled those of cardiac muscle. Skin from the experimental animals was dry and flaky; loss of eyelashes with facial edema and petechiae (small hemorrhages) were commonly observed. Microscopic changes in the skin are illustrated in Figure 55. Along with facial edema, anasarca (widespread edema of abdomen and extremities) was commonly observed.

The rat also has been studied extensively (Gupta et al. 1973; Norback and Allen 1973; Kociba et al. 1978; Greig and Osborne 1978). Gross pathological observation indicated that rats died with jaundiced ears, subcutaneous tissues, and visceral organs. Uterine size was decreased, and there was a generalized loss of subcutaneous and abdominal fat. The liver and spleen were small, and the liver was friable and dark tan. All thymuses were markedly atrophied, and hemorrhages were present in the gastrointestinal tract and meninges.

Microscopic observation showed a relative depletion of lymphoid cells in the spleen and lymph nodes, and markedly smaller thymic lobules with no demarcation between the cortex and medulla. Rats given large doses of 2,3,7,8-TCDD showed marked changes in liver cellular morphology and architecture, as illustrated in Figures 56 through 59. Hepatocytes were round and large, and the hepatic cords were disorganized. Increased mitoses were seen in the liver parenchyma (mass of cells), and some areas contained hepatocytes with seven to ten nuclei (see Figure 56). Individual hepatocytes showed proliferation of smooth endoplasmic reticulum and often distorted cell membranes. Also, the number of lipid droplets are increased. Atretic (degenerative and distorted) changes were

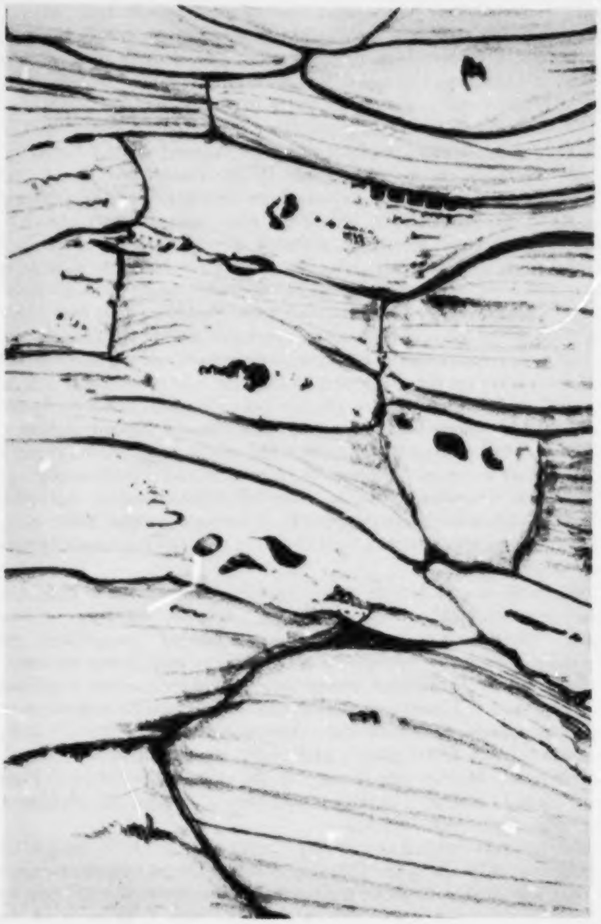

Figure 53. Drawing of tissue from heart of monkey fed 2,3,7,8-TCDD; tissue fixed with formalin and stained with hematoxylin and eosin. Muscle cells are hypertrophic with enlarged and distorted nuclei. X115.

Source: Redrawn from Norback and Allen 1973.

noted in the ovarian follicles, and mucosol folds and glandular structures in the uterus were atrophied. Epithelial cells of the renal tubules were foamy and vacuolated with numerous hyaline droplets. Moderate to marked degenerative changes were noted in the epithelial cells of the thyroid follicles, and there were papillary projections into the lumen of the follicles. Focal hyperplasia (increased cell number) was noted in the terminal bronchioles of the lung (Figure 60). Congestion and elongation of the intestinal villi also were noted.

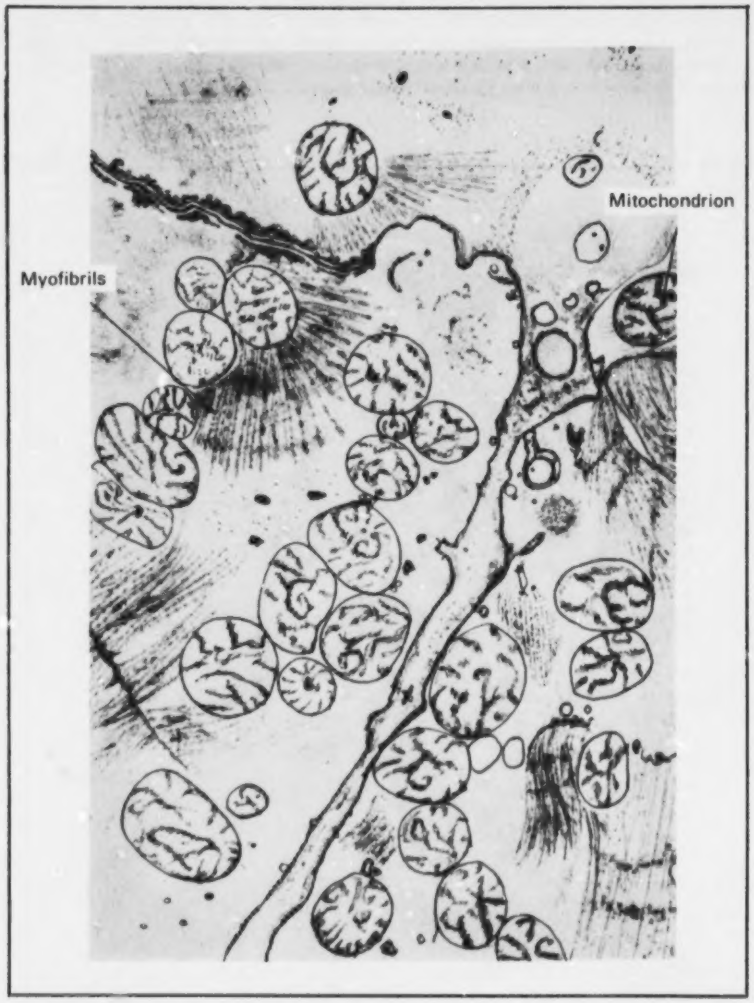

Figure 54. Drawing of heart tissue from monkey fed 2,3,7,8-TCDD. Myofibrils of dilated cardiac fibers are separated, and the mitochondria are moderately swollen. Tissue fixed with Veronal acetate-buffered osmium tetroxide solution and stained with uranyl acetate. X9700.
Source: Redrawn from Norback and Allen 1973.

Pathology of chickens exposed to dioxins is similar to that observed in other animals (Norback and Allen 1973). Chickens succumbed very rapidly, with hydropericardium (fluid in sac surrounding heart), hydrothorax (fluid in chest cavity surrounding lungs), and ascites. They also developed liver necrosis, hypoplastic testes, altered capillary permeability, and decreased hematopoiesis.

Gupta et al. (1973) report pathologic findings in guinea pigs and mice exposed to 2,3,7,8-TCDD. In guinea pigs, mitotic figures and loss of lipid vacuoles were observed in the zona fasiculata, along with atrophy of the zona glomerulosa of the adrenals. Guinea pigs also had widespread hemorrhages in the subserosal region of the gastrointestinal tract, bladder, lymph nodes, and adrenals. Pathologic findings observed in mice are similar to those noted in other animals.

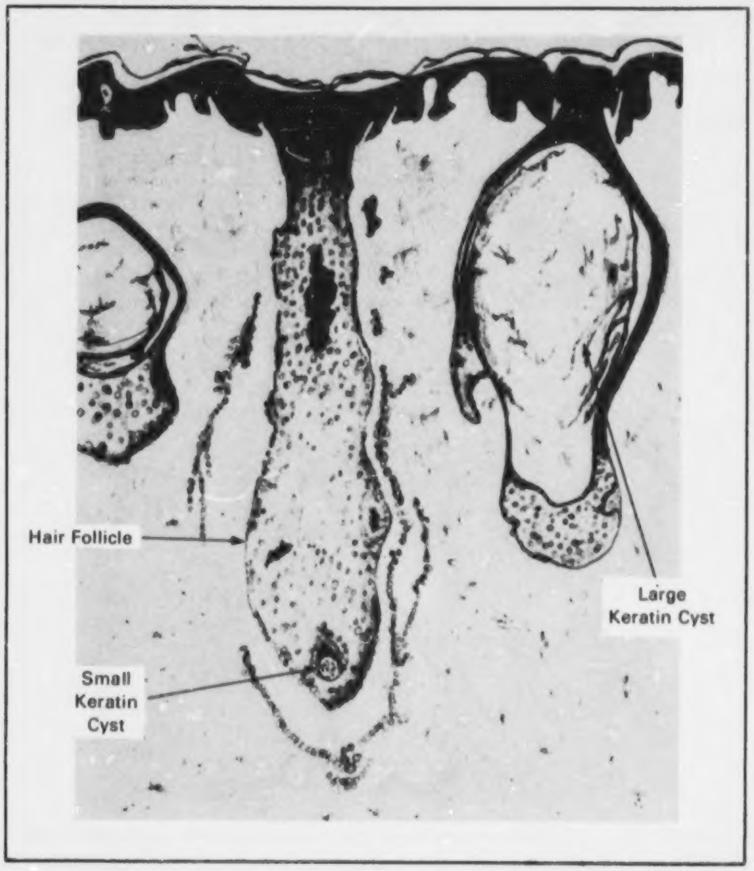

Figure 55. Drawing of section of skin of monkey fed 2,3,7,8-TCDD. Note the presence of keratin cysts and the lack of a hair shaft in the hair follicle. Tissue fixed with formalin and stained with hematoxylin and eosin. X15.

Source: Redrawn from Norback and Allen 1973.

ACUTE TOXICITY

The acute and subacute toxic potential of 2,3,7,8-TCDD in animals relative to some other chlorodioxins and pesticides is illustrated in Tables 39 and 40. As the tables indicate, 2,3,7,8-TCDD is a highly toxic material, several orders of magnitude more potent than many pesticides. Some consider it to be the most toxic small molecule made by man (Poland and Kende 1976).

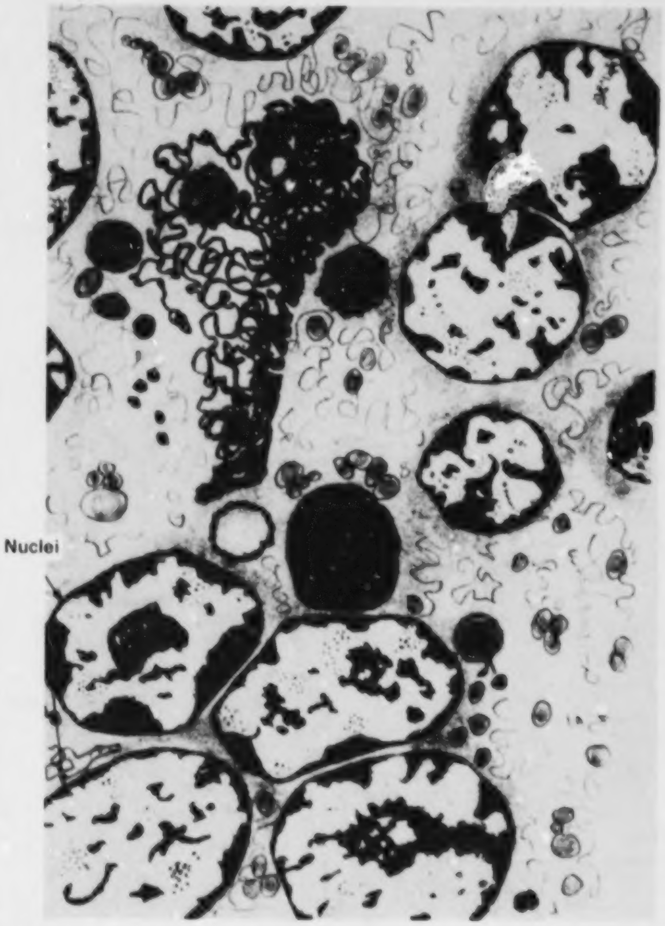

Figure 56. Drawing of part of a multinucleated liver cell from a female rat given 0.1 μg of 2,3,7,8-TCDD/kg/day for 2 years. Uranyl acetate-lead citrate stain. X1620.

Source: Redrawn from Kociba, et al. 1978.

Comparative Lethal Doses

Table 40 lists the LD_{50} values for various substituted dibenzo-*p*-dioxins. The 2,3,7,8-TCDD isomer is 3 to 100 times more potent than the other tetrachlorinated isomers (Dow 1978). In comparison with 2,3,7,8-TCDD, the 1,3,6,8- and 1,3,7,9-tetrachlorinated isomers have little biological activity (Rappe 1978). Both octachlorodioxin and the unsubstituted dioxin are relatively nontoxic. Dioxin

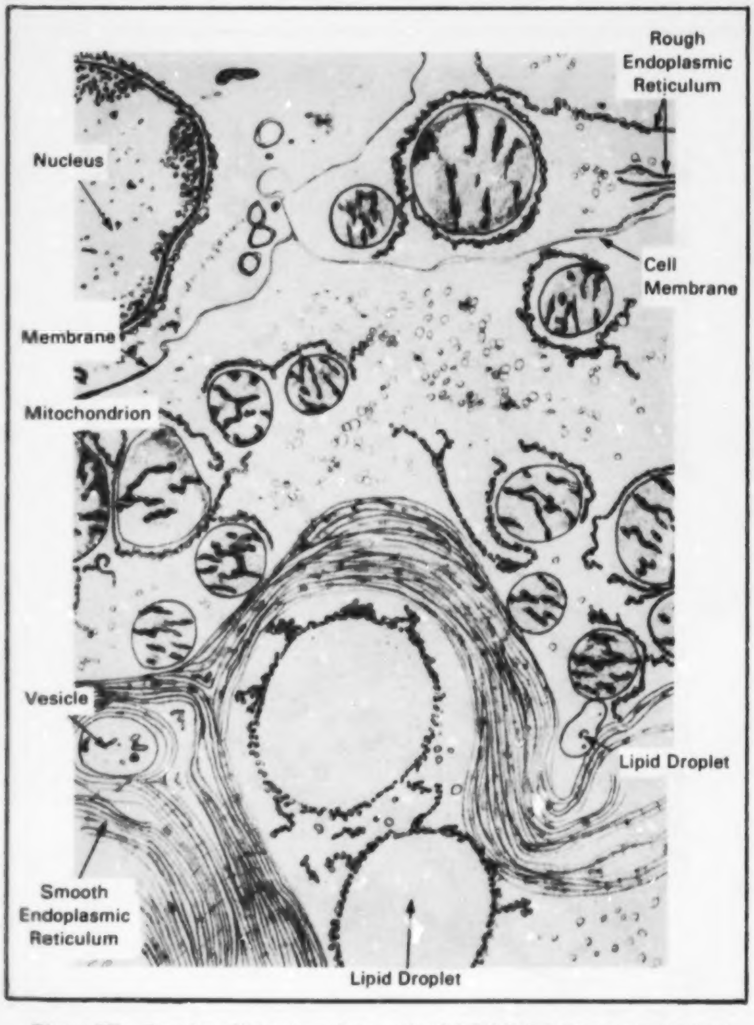

Figure 57. Drawing of liver tissue from rat fed 2,3,7,8-TCDD. Tissue sample fixed in Veronal acetate-buffered osmium tetroxide solution and stained with uranyl acetate. X20400.

Source: Redrawn from Norback and Allen 1973.

structure-activity relationships are discussed in a later subsection. The LD_{50} values for 2,3,7,8-TCDD in rats, guinea pigs, and rabbits are presented in Table 41. The male guinea pig appears to be the most sensitive, having an LD_{50} of 0.0006 mg/kg (0.6 μg/kg). The LD_{50} values in monkeys exposed to a single oral dose range from 50 to 70 μg/kg body weight (McConnell, Moore, and Dalgard 1978). In mice, the LD_{50} is 0.2837 mg/kg body weight (McConnell et al. 1978).

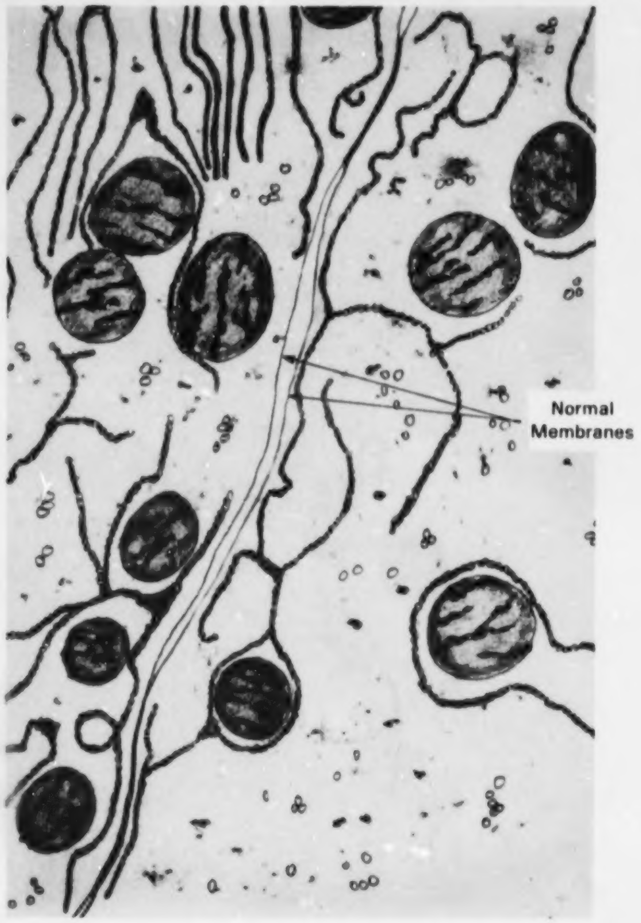

Figure 58. Drawing of normal membrane junctions from the periportal region of a test animal 42 days after administration of 200 μg/kg 2,3,7,8-TCDD. Uranyl acetate and lead citrate stain. X16000.

Source: Redrawn from Greig and Osborne 1978.

Target organs for the acute toxic effects of TCDD in commonly studied laboratory animals are listed in Table 42. All species of animals studied by Moore et al. (1976) showed severe thymus involution and testicular degeneration. Reduction in the white pulp of the spleen combined with bone-marrow hypoplasia (decreased cell number) were other common effects. Mice exhibited the greatest degree of liver toxicity, and female monkeys showed the most skin lesions and bile-

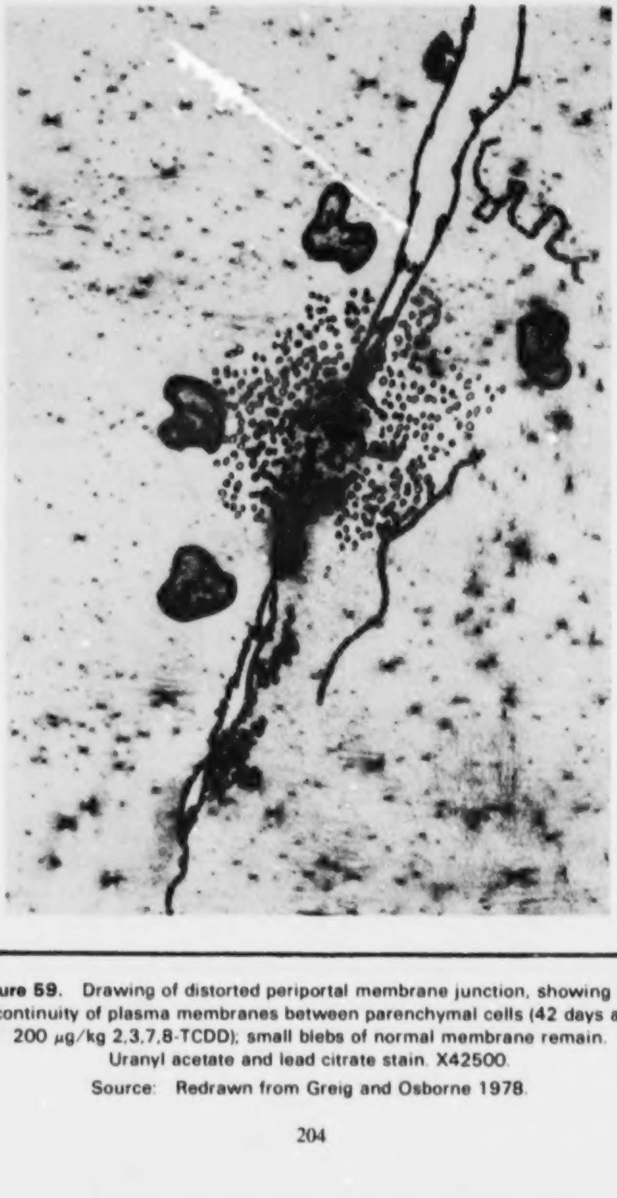

Figure 59. Drawing of distorted periportal membrane junction, showing loss of continuity of plasma membranes between parenchymal cells (42 days after 200 µg/kg 2,3,7,8-TCDD); small blebs of normal membrane remain. Uranyl acetate and lead citrate stain. X42500.

Source: Redrawn from Greig and Osborne 1978.

duct hyperplasia. Ascites was common in monkeys, but was more prominent in mice. Hyperplasia of the renal pelvis and urinary bladder was common in guinea pigs. Gastrointestinal hemorrhages were common in both mice and guinea pigs.

Aquatic Toxicity

No data are available concerning the acute toxicity of 2,3,7,8-TCDD on saltwater organisms, and there are only scant data relative to freshwater aquatic life

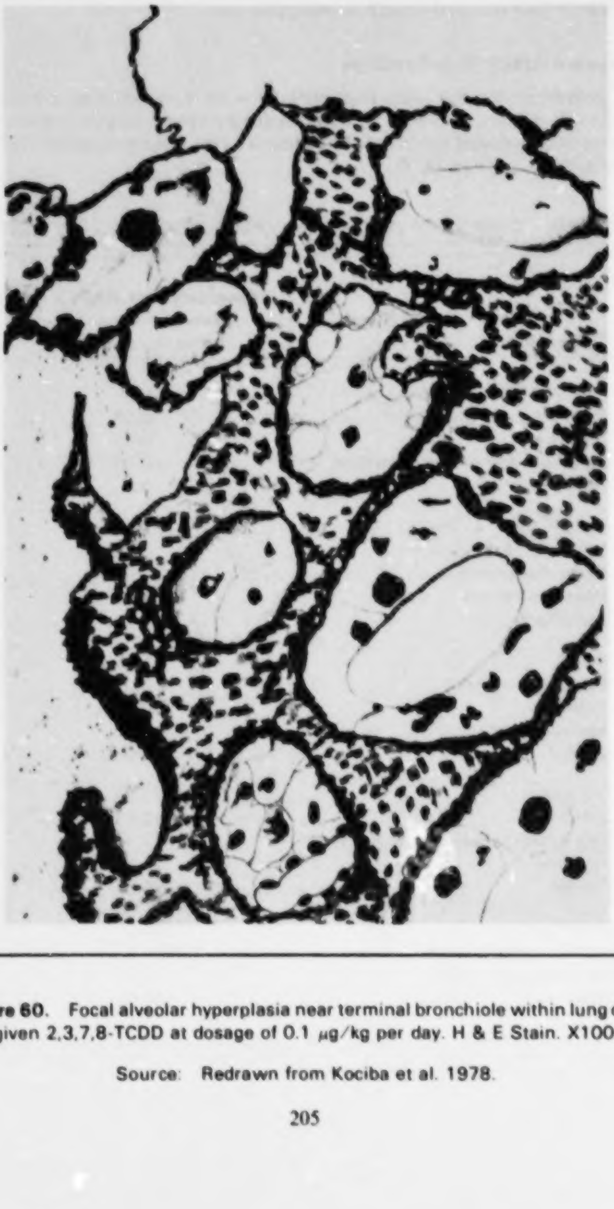

Figure 60. Focal alveolar hyperplasia near terminal bronchiole within lung of rat given 2,3,7,8-TCDD at dosage of 0.1 μg/kg per day. H & E Stain. X100.

Source: Redrawn from Kociba et al. 1978.

(U.S. EPA 1978c). Exposures of fish and invertebrate species to the dioxin in water and food and by intraperitoneal injection have demonstrated a variety of adverse effects at very low concentrations. Model ecosystem studies have demonstrated bioconcentration factors for 2,3,7,8-TCDD of 3,600 and 26,000 over a period of 3 to 31 days (Isensee and Jones 1975). Exposure of coho salmon to an aqueous concentration of 0.000056 μg/liter under static conditions for 96 hours resulted in 12 percent mortality, whereas mortality of control fish was 2 percent (Miller, Norris, and Hawks 1973). In the same study, all coho salmon exposed to 0.056 μg/liter for 24 hours were dead within 40 days. Isensee (1978) reports that 3 ppt of 2,3,7,8-TCDD is acutely toxic to mosquito fish.

Structure-Activity Relationships

The general structure-activity relationships of dibenzo-*p*-dioxins are presented earlier in this section. Briefly, at least one hydrogen atom and a minimum of three laterally placed halogen atoms must be present in the dioxin structure for it to be toxic (Kende and Wade 1973).

TABLE 39. TOXICITIES OF ORGANIC PESTICIDES AND 2,3,7,8-TCDD[a]

Compound	Maximum dose producing no observed adverse effect (mg/kg per day)
2,3,7,8-TCDD	10^{-6}
Disolfoton and phorate	0.01
Diazinon	0.02
Parathion and methyl parathion	0.043
Aldicarb	0.1
Malathion	0.2
Silvex (2,4,5-TP)	0.75
Hexachlorobenzene	1.0
Hexachlorophene	1.0
Toxaphene	1.25
MPCA	1.25
Pentachlorophenol	3.0
Butachlor	10.0
Methoxychlor	10.0
2,4,5-T	10.0
Bromacil	12.5
2,4-D	12.5
Ortho- and paradichlorobenzene	13.4
Atrazine	21.5
Captan	50.0
Arachlor	100.0
Methyl methacralate	100.0
Di-*n*-butyl phthalate	110.0
Styrene	133.0

a—Source: National Academy of Science 1977.

TABLE 40. ACUTE TOXICITIES OF DIOXINS[a]

	LD$_{50}$ (μg/kg)[b]	
Substitutions with chlorine	Guinea pigs	Mice
None[c]		>50 × 10^3 (i.p.)[e]
2,8	>300,000.0	
2,3,7	29,444.0	>3,000.0
2,3,7,8	0.6-2.0	283.7
1,2,3,7,8	3.1	337.5
1,2,4,7,8	1,125.0	>5,000.0
1,2,3,4,7,8	72.5	825.0
1,2,3,6,7,8	70-100	1,250.0
1,2,3,7,8,9	60-100	>1,440.0
1,2,3,4,6,7,8	>600;7180[d]	
1,2,3,4,6,7,8,9[c]		>4 × 10^6
1-NO$_2$-3,7,8	>30,000.0	
1-NH$_2$-3,7,8	>30,000.0	
1-NO$_2$-2,3,7,8	47.5	>2,000.0
1-NH$_2$-2,3,7,8	194.2	>4,800.0

a—Unless otherwise noted, taken from McConnell et al. 1978.

b—All values are for oral doses unless noted; test period is 30 days.

c—World Health Organization, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. 15:69-70, August 1977.

d—EPA-RPAR on Pentachlorophenol. Federal Register 43(202):48454, October 18, 1978.

e—Interperitoneal.

TABLE 41. ACUTE TOXICITIES OF 2,3,7,8-TCDD FOR VARIOUS SPECIES[a]

Species	Sex	Route of exposure	Dosage (LD$_{50}$ mg/kg)
Rat	Male	Oral	0.0220
	Female	Oral	0.0450
Guinea pig	Male	Oral	0.0006
	Male	Oral	0.0021
Rabbit	Female and male	Oral	0.1150
	Female and male	Dermal	0.2720
	Female and male	Interperitoneal	>0.2520

a—Source: Schwetz et al. 1973.

TABLE 42. SUMMARY OF ACUTE TOXICITY EFFECTS OF 2,3,7,8-TCDD[a]

	Mice	Guinea pigs	Monkeys (female)
Thymus involution	+++	+++	+++
Spleen reduction (white pulp)	+	+	+
Bone-marrow hypoplasia	±	++	+
Liver, megalocytosis/degeneration	+++	-	-
Bile-duct hyperplasia	±	±	+++
Testicular degeneration	++	+++	N/A
Renal-pelvis hyperplasia	-	++	+
Urinary-bladder hyperplasia	-	++	-
Adrenal-cortical atrophy (Zona Glomerulus)	-	++	-
Hemmorhage: Intestinal	+	+	-
Adrenal	-	++	-
Ascites	++	-	+
Cutaneous lesions	-	-	+++

[a]—Source: Moore et al. 1976. Key as follows:
- no effects
+ mildly affected
++ moderately affected
+++ severely affected

Studies have shown that a dioxin's ability for enzymatic induction correlates well with its toxic potential and thus its structure. In one study, age- and sex-related differences in hepatic mixed-function oxidase activity in rats apparently were inversely correlated with the 20-day LD_{50} of 2,3,7,8-TCDD (Beatty et al. 1978). The study also examined the effects of administering inducers and inhibitors of the hepatic mixed-function oxidase enzyme systems of the 20-day LD_{50} of 2,3,7,8-TCDD in rats. In all cases, there was an inverse relationship.

CHRONIC TOXICITY

Although chloracne is a common indicator of 2,3,7,8-TCDD exposure in humans and some animals, chronic exposure to this dioxin can affect many organ systems. In addition to chloracne, another dermatologic manifestation of exposure is porphyria cutanea tarda (PCT), a photosensitive dermatosis caused by altered porphyrin metabolism. Hepatic (liver) toxicity resulting from prolonged exposure to 2,3,7,8-TCDD is common in animal models and has been observed in human workers after industrial exposures. In animal models, the dioxin has caused damage to renal (kidney) tubular epithelium and caused alteration in levels of serum gonadotropin (pituitary hormones influencing reproductive organs). A profound deficit in cell-mediated immunity is produced in experimental animals exposed to 2,3,7,8-TCDD in the perinatal period. Along with thymic atrophy, exposure to 2,3,7,8-TCDD leads to a depletion of cells in the spleen, lymph nodes, and bone marrow. Hypertrophic gastritis has been observed frequently in exposed monkeys. Alterations in lipid metabolism produced by 2,3,7,8-TCDD exposure may greatly increase the risk of atherogenesis in occupationally exposed workers. Neuropsychiatric symptoms including neurasthenia (depressive syndrome with vegetative symptoms) and peripheral neuropathies have been attributed to 2,3,7,8-TCDD exposure. These various aspects of chronic toxicity are discussed in the following subsections.

Dermatologic Effects

Dermatologic diseases are perhaps the most sensitive indicators of 2,3,7,8-TCDD exposure and toxicity in humans. Although chloracne is the most frequently observed dermatosis, PCT has been observed in as many as 10 percent of a group of occupationally exposed workers (Purkyne et al. 1974).

Chloracne—

Chloracne, which is characterized by comedones, keratin cysts, pustules, papules, and abscesses, is a classical sign of 2,3,7,8-TCDD exposure in humans (U.S. NIEHS IARC 1978). Chloracne can be caused by ingestion, inhalation, or skin contact with chlorodibenzodioxins, and the disease may clear in a few months or persist for as long as 15 years (Crow 1978). All chlorodibenzodioxins that are acnegenic are also systemic toxins, but the external dose needed to produce chloracne is far lower than that needed to cause systemic toxicity (Crow 1978). Chloracne, which can be an extremely refractory form of occupational acne, was first described by Von Bettman in 1897 (Taylor 1974). The symptoms may appear weeks or months after the initial exposure to chlorodibenzodioxins. Rabbits can be used to test the acnegenicity of a chlorodibenzodioxin, because these compounds induce acneform lesions when applied to the skin of rabbit ears (Kimmig and Schulz 1957).

Kimmig and Schulz (1957) provided a detailed description of the clinical manifestations of chloracne that developed in 31 workers in a German plant producing 2,4,5-T in 1954. In heavily exposed workers, dermatitis of the face accompanied by erythma and swelling was first observed. As these symptoms faded, acneform lesions appeared on the face and later on other parts of the body. In most workers, the initial manifestations of chloracne were patches of open comedones (blackheads) followed by pustules in the zygomatic region (cheeks) of the face. Upon initial examination, the observed skin changes included many blackheads, pinhead- to pea-sized closed comedones (whiteheads), associated follicular hyperkeratosis, inflamed pimples, pustules, and large boils. The face, ears, throat, and neck were affected in all cases; in severe cases, lesions were encountered on the breast, back, epigastrium (skin of upper abdomen), genitals, and extensor surfaces of the arms and thighs.

Porphyria Cutanea Tarda (PCT)—

Porphyria cutanea tarda (PCT) is a skin condition that usually occurs as a photosensitive dermatosis and is characterized by development of vesiculobullous (blistering) lesions over exposed areas (Benedetto and Taylor 1978). The dermatosis is precipitated by minor trauma, and may result in areas of healed bullae, crusts, scars, and milia. Hyperpigmentation, hypertrichosis (excessive growth of hair), and schlerodermoid (tightening of skin over the fingers) changes can also occur, along with dark red urine (Benedetto and Taylor 1978). Animal studies have shown that 2,3,7,8-TCDD is the porphyrinogenic compound formed during the manufacture of 2,4,5-T. Jones and Sweeney (1977) have shown that uroporphyrinogen decarboxylase (UD) levels can be depressed in rats given

2,3,7,8-TCDD. Their results indicate that the dioxin depresses UD levels sufficiently to produce the biochemical disturbance of PCT. Sweeney (1979) notes that iron-deficient mice are protected from porphyria produced by 2,3,7,8-TCDD exposure.

Hepatic Effects

The hepatotoxicity of 2,3,7,8-TCDD appears to be dose-dependent, and the severity of any changes produced varies among species (Gupta 1973). In rats and rabbits, hepatic necrosis produced by this compound is probably a contributing cause of death, whereas hepatic necrosis and liver insufficiency are less extensive in mice and are minimal relative to these disorders observed in guinea pigs and monkeys (U.S. NIEHS IARC 1978). Van Miller et al. (1977) noted liver necrosis and bile duct hyperplasia in a group of rats fed 1.0, 0.6, and 0.05 ppm 2,3,7,8-TCDD for 65 weeks. In a 13-week toxicity study in which the dioxin was administered orally to rats, doses of 1.0 μg/kg per day increased the levels of serum bilirubin and alkaline phosphatase and caused pathologic changes in the liver; doses of 0.1 μg/kg per day caused a slight degree of liver degeneration (Kociba et al. 1976). The histopathologic changes in rat liver resulting from 2,3,7,8-TCDD exposure were described earlier.

Renal Effects

Several recent studies have examined the effects of 2,3,7,8-TCDD upon renal function in the rat (Anaizi et al. 1978; Hook et al. 1978). Anaizi et al. studied the steady-state secretion rate of phenosulfonphthalein (PSP) in rats pretreated with 10 μg/kg of 2,3,7,8-TCDD 5 to 7 days prior to in vivo measurements. The results were as follows:

- A significant increase in the tubular secretion rate of PSP occurred at low plasma levels of PCP.
- There was no increase in the maximum secretory capacity for PSP (Tm-PSP).
- A significant change in the glomerular filtration rate from 1.17 to 0.90 ml/min per gram of wet kidney weight was observed in treated rats without a change in the mean arterial pressure.

Anaizi et al. inferred from this study that glomerular structures in rats are highly sensitive to 2,3,7,8-TCDD.

Hook et al. (1978) examined renal accumulation of *p*-aminohippurate (PAH) and *N*-methyl-nicotinamide (NMN) in rats given 10, 25, or 50 μg/kg 2,3,7,8-TCDD. In the 10 μg/kg dose group, only NMN accumulation was slightly decreased at 7 days. At 25 μg/kg, the capacity of renal tissue to transport both PAH and NMN was reduced 7 days after exposure. The GFR and effective renal plasma flow were decreased in rats after doses of 25 or 50 μg/kg. Volume expansion did not alter this relationship in the study. Thus these two independent studies confirmed the ability of 2,3,7,8-TCDD to decrease renal function in the rat.

Endocrine Effects

It has been known for some time that 2,3,7,8-TCDD exposure in man is associated with hormonal imbalances that lead to acne, hirsutism, and loss of libido. Recently it has been shown that 2,3,7,8-TCDD can also have a dramatic effect upon hormones involved in reproduction. A recent study has indicated a suppressive effect upon testicular microsomal cytochrome P-450 content in guinea pigs (Piper 1979). Another study has shown that 2,3,7,8-TCDD increases serum thyroid stimulating hormone in humans 4- to 5-fold, and preliminary observations indicate that serum levels of prolactin and follicle stimulating hormone are affected in rats following treatment with the dioxin (Gustafsson and Ingelman-Sundberg 1979). Testosterone hydroxylation in the 2 β- and 16 α-positions has been reduced by 50 percent in rats receiving less than 1 μg/kg of 2,3,7,8-TCDD orally (Hook et al. 1975). Similarly, exposures of female rats have shown 3- to 5-fold increases in the following enzyme activities (Gustafsson and Ingelman-Sundberg 1979):

1. 7 α- and 6 β-hydroxylases active on 4-androstene-3,17-dione;
2. 7 α- and 2 β-hydroxylases active on 5 α-androstane-3α, 17 β-diol; and
3. 16 α- and 6 β-hydroxylases active on 4-pregnene-3,10-dione.

One recent study examined hormonal alterations in female rhesus monkeys fed a diet containing 500 ppt of 2,3,7,8-TCDD per day for 9 months (Barsotti, Abrahamson, and Allen 1979). Steroid analysis at 6 months showed alterations in five of seven animals treated. Progesterone levels in three animals decreased to 72.4 percent, 51.9 percent, and 47.3 percent of their pretreatment values. During the same interval, estradiol levels in two of these animals also decreased to 50.4 percent and 43.2 percent of the control values. The remaining two animals with abnormalities showed anovulatory patterns for both steroids. Estradiol never rose above 30 pg/ml of serum and progesterone remained below 400 pg/ml of serum throughout the menstrual cycles. After these analyses, all animals were bred. All of the control animals conceived and gave birth to healthy infants. The two dioxin-treated animals in which estradiol and progesterone levels had remained normal did conceive, but one animal aborted the conceptus. Several other treated monkeys conceived, but all subsequently aborted. The one dioxin-treated animal that carried a fetus to term delivered a normal, healthy infant. After nine months, the only monkey that had showed hormonal alterations and survived was placed back on the control diet and subsequently delivered a normal, healthy infant.

Immunologic Effects

Exposure to 2,3,7,8-TCDD has caused thymus atrophy in all mammalian species studied. As illustrated in Table 43, impairment of cellular immunity has been a constant finding in studies of the effects of this dioxin on the immune system of animals. Thymus (T-)-dependent lymphocytes are most affected by the exposure; however, T-helper-cells are less compromised than other types of T-cells (Faith and Luster 1977).

Suppression of cell-mediated immunity appears to be age-related in the mouse and rat; perinatal exposure causes the greatest effect (Luster et al. 1978). It is important to recognize that TCDD can produce immunosuppressive effects at exposure levels too low to produce clinical or pathological changes (Thigpen et al. 1975).

Many studies have examined the effects of exposure to 2,3,7,8-TCDD on impairment of cell-mediated immunity. Several studies have examined the effects of either postnatal or both pre- and postnatal exposure of rat pups by maternal dosing (Faith and Luster 1977; Luster et al. 1978). Results indicated that cell-mediated immune functions were depressed up to 133 days of age in both groups but less severely in animals exposed only postnatally. In addition, the ratio of thymus to body weight was depressed up to 145 days of age in prenatally exposed rats, but the ratio was suppressed only up to 39 days of age in the postnatally exposed group. These studies established that depression of T-cell function is selective in that helper T-cell function was spared. Vos and Moore (1974) demonstrated that cell-mediated immunity in 1-month old rats was depressed only when toxic doses of 2,3,7,8-TCDD were administered. In vitro testing has demonstrated that DNA, RNA, and protein synthesis in splenic lymphocytes is severely inhibited when mouse spleens are only briefly exposed to 10^{-7} millimolar solutions of 2,3,7,8-TCDD (Luster 1979a).

TABLE 43. EFFECTS OF IN VIVO 2,3,7,8-TCDD EXPOSURE ON FUNCTIONAL IMMUNOLOGICAL PARAMETERS[a]

Species	Parameter	Effect[b]	Reference
Guinea pig	Delayed type hypersensitivity	$+^{c}$	Vos et al. 1973
Rat	Delayed type hypersensitivity	$+^{d}/-^{c}$	Moore and Faith 1976; Vos et al. 1973
Rat	Graft versus host activity	$+^{d}$	Vos and Moore 1974
Mouse	Graft versus host activity	$+^{c}/-^{e}$	Vos and Moore 1974; Vos et al. 1973
Rat, mouse	Rejection of skin allografts	$+^{d}$	Vos and Moore 1974
Rat	Lymphocyte transformation by PHA and Con A	$++^{d}$	Vos and Moore 1974; Moore and Faith 1976
Mouse	Lymphocyte transformation by PHA	$+^{c}/-^{e}$	Vos and Moore 1974
Guinea pig	Antibody response to tetanus toxoid	$-^{c,f}/+^{c,g}$	Vos et al. 1973
Rat	Antibody response to bovine γ-globulin	$-^{d,f}/-^{d,g}$	Moore and Faith 1976

a—Source: Vos et al. 1978.
b—Denotes the suppressive effect on immunological parameters. Key: + = slight; ++ = moderate effect; – = no effect.
c—Treatment of young animals.
d—Treatment during the perinatal period.
e—Treatment of adult animals.
f—Primary antibody response.
g—Secondary antibody response.

Multiple studies have examined the effects of 2,3,7,8-TCDD exposure upon in vivo susceptibility to pathogenic organisms. Thigpen et al. (1975) administered sublethal levels of the dioxin to mice and then subjected them to challenges with *Salmonella bern* and *Herpesvirus suis*. At dose schedules of 1 μg/kg weekly for 4 weeks, salmonella infection led to significant increases in mortality and reduction of time from infection to death. The dioxin exposure had no apparent effect upon the outcome of infection with *Herpesvirus suis*. Other researchers found that mouse pups from mothers fed up to 5 ppb of 2,3,7,8-TCDD withstood a live *Listeria* challenge as well as did the controls; however, maternal feeding at 2,3,7,8-TCDD levels as low as 1 ppb rendered offspring more sensitive to challenge with endotoxin (cell walls of gram negative bacteria) (Thomas and Hinsdill 1979). Nonspecific killing and phagocytosis* of *Listeria monocytogenes* in mice were not influenced by administration of 2,3,7,8-TCDD (Vos et al. 1978). In the same study, treatment with the dioxin did not affect macrophage reduction of nitro-blue-tetrazolium, and the authors speculated that endotoxin sensitivity in treated animals is not the result of altered phagocytic function of macrophages. Similarly, challenge with pathogenic streptococcus in aerosol form led to similar mortality rates among treated mice and controls (Campbell 1979).

Humoral immunity and B-lymphocyte function are resistant to the toxic effects of 2,3,7,8-TCDD. Faith and Luster (1977) found that humoral immune responses to bovine gamma globulin were not suppressed in rats treated with the dioxin. Luster (1979b) then demonstrated that T-lymphocytes are much more susceptible to dioxin-induced immuno-suppression than B-lymphocytes with mitogens specific for lymphocyte subpopulations. By measuring the antibody response against tetanus toxoid in guinea pigs, Vos et al. (1973) showed only a slight decrease in humoral immunity in 2,3,7,8-TCDD-treated animals. Thomas and Hindsill (1979) demonstrated normal primary and secondary antibody responses in treated mice.

Hematologic Effects

One of the major target organs for TCDD toxicity is the hematopoietic system. Although many species have been studied, anemia has been observed only in rhesus monkeys (Allen 1967). This anemia was of an aplastic type (characterized by lack of cells in bone marrow) and was accompanied by atrophic bone marrow. The only abnormalities of the hematopoietic system noted in 2,3,7,8-TCDD-treated rats have been thrombocytopenia (increased numbers of platelets) and terminal elevated packed red cell volumes secondary to hemoconcentration (Weissberg and Zinkl 1973). In this study, the platelet counts of treated rats were significantly reduced and their bone marrows contained normal numbers of megakaryocytes. Zinkl et al. (1973) studied the hematologic effects of exposing guinea pigs and mice to TCDD. The leukocyte and lymphocyte counts in mice given a single oral dose of as little as 1.0 μg/kg TCDD were significantly lower after 1 week. A similar relationship was observed in guinea pigs treated with tetanus toxoid or *Mycobacterium tuberculosis*. In mice, the lymphopenia (decreased numbers of lymphocytes) was reversed 5 weeks after exposure to the dioxin.

Gastrointestinal Effects

Two studies have explored the effect of dibenzo-*p*-dioxins upon intestinal absorption of nutrients. Ball and Chhabra (1977) used in vitro everted sac and in situ closed loop techniques to study the effect of a toxic dose of 2,3,7,8-TCDD (100 μg/kg po) on adult male rats. Glucose uptake declined during the first few hours following dosage, rose above controls between one and two weeks, and declined again after three weeks. Leucine uptake was depressed throughout the study.

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*The process by which cells engulf and destroy foreign material.

Madge (1977) studied the effects of 2,3,7,8-TCDD and OCDD on function of the small intestine in mice. He found that absorption of D-glucose decreased following a single oral dose of each of the compounds. No effect was noted on the absorption of D-galactose, L-arginine, or L-histidine. Total fluid transfer was generally unaffected by treatment with either compound, and D-mannose, an exogenous energy source, abolished the apparent malabsorptive effects of D-glucose in treated animals.

Neuropsychiatric Effects

Two studies have examined the neuropsychological function of rats exposed to 2,3,7,8-TCDD. Creso et al. (1978) found that exposure induced irritability, aggressiveness, and restlessness in rats, without acquisition or loss of a conditioned avoidance reflex. In this study, the dioxin stimulated the activity of adenyl cyclase in the rat brain striatum and hypothalmus in vitro. It also enhanced the stimulatory effect of dopamine on striatal adenyl cyclase; however, this action was blocked by haloperidol. The study also showed that 2,3,7,8-TCDD acted synergistically with histamine in stimulating the hypothalmic adenyl cyclase.

Elovaara et al. (1977) showed that treatment with 2,3,7,8-TCDD caused: 1) an increase in acid proteinase activity in the brains of normal Wistar rats, 2) reduction of RNA and protein contents in heterozygous Gunn rats, and 3) no changes in homozygous Gunn rats.

Purkyne et al. (1974) found various psychiatric and neurological complaints in a cohort of 55 workers occupationally exposed to 2,3,7,8-TCDD. Seventeen subjects showed neurological abnormalities. The most common disorder was polyneuropathy of the lower extremities (confirmed by electromyography). Most of these patients suffered from psychiatric disorders such as severe neurasthenia syndromes with vegetative symptoms. These workers complained of weakness and pain in the lower extremities, somnolence, insomnia, excessive perspiration, headache, and various sexual disorders.

DEVELOPMENTAL EFFECTS

A brief review of the pertinent nomenclature is given here to characterize the several developmental effects discussed in this section. The terms embryotoxicity and fetotoxicity denote all transient or permanent toxic effects induced in an embryo or fetus, regardless of the mechaniam of action. These are the most comprehensive terms. A special fetotoxic effect is teratogenicity, which is defined as an abnormality originating from impairment of an event that is typical in embryonic or fetal development. For example, fetal growth retardation is a fetotoxic but not a teratogenic effect of 2,3,7,8-TCDD (Neubert et al. 1973).

The first clue to the teratogenic and fetotoxic potential of 2,3,7,8-TCDD resulted from a National Cancer Institute study begun in 1964 to evaluate the carcinogenic and teratogenic potential of a number of herbicides (Collins and Williams 1971). In this study, 2,4,5-T and 2,4-D were shown to induce increased proportions of abnormal fetuses in hamsters. Courtney (1970) demonstrated the teratogenicity of 2,4,5-T containing approximately 30 ppm of 2,3,7,8-TCDD in two strains of mice. Subsequent investigations studied the fetotoxicity and teratogenicity of both 2,4,5-T and 2,3,7,8-TCDD in a number of species.

Teratogenicity

Courtney (1970) showed that 2,4,5-T containing 2,3,7,8-TCDD increased the incidence of cleft palate in both C57BC/6 and AKR mice. Neubert et al. (1972), using the purest available sample of 2,4,5-T, showed that at doses higher than 20 mg/kg given orally during days 6 to 15 of gestation, the frequency of cleft palate was significantly increased in NMRI mice. The maximal teratogenic effect was produced when the drug was administered on days 12 or 13 of gestation. In the same study, doses exceeding 1 μg/kg of 2,3,7,8-TCDD produced an increased rate of cleft palate; maximal teratogenicity occurred with administration on days 8 and 11 of gestation. Although Courtney and Moore (1971) found no potentiation of teratogenicity with combinations of 2,4,5-T and 2,3,7,8-TCDD, Neubert and co-workers found that 1.5 ppm of 2,3,7,8-TCDD administered with 30 to 60 mg/kg 2,4,5-T potentiated the increase in cleft palate frequency. Moore and co-workers (1973) found that the mean average incidence of cleft palate was 55.4 percent in mice exposed to 3 μg/kg 2,3,7,8-TCDD on days 10 to 13 of gestation. In 1976, the threshold teratogenic dose of 2,3,7,8-TCDD in CF-1 mice was estimated to be 0.1 μg/kg per day (Smith, Schwetz, and Nitchke 1976). In golden hamsters, oral administration of 2,4,5-T containing dioxin on days 6 to 10 of gestation increased the incidence of absence of the eyelid (Collins and Williams 1971). Although 2,3,7,8-TCDD is fetotoxic in primates at doses as low as 50 ppt, it has not been shown to be teratogenic in this species (Schantz et al. 1979).

Fetotoxicity and Embryotoxicity

In general, 2,4,5-T and 2,3,7,8-TCDD produce fetotoxicity at doses that do not produce teratogenic effects in a wide variety of species. Fetotoxic effects of 2,4,5-T containing 2,3,7,8-TCDD were first noted in Courtney's original work (1970). Both species of mice studied showed increased incidences of cystic kidneys, while in rats, fetal gastrointestinal hemorrhages and increased ratios of liver to body weight were also noted. Highman and Schumacher (1977) later demonstrated that cystic kidneys in mice exposed to 2,4,5-T containing 2,3,7,8-TCDD were due to retardation in fetal renal development and downgrowth of the renal papilla into the pelvis. The results of this study demonstrated a retarded development of fetal renal alkaline phosphatase, and thus support the hypothesis that cystic kidneys in mice are a fetotoxic and not truly a teratogenic effect. Moore et al. (1973) proved that prenatal and postnatal kidney anomalies had a common etiology, and the incidence and degree of hydronephrosis* was a function of dose and of the length of exposure of a target organ. Other fetotoxic effects of 2,4,5-T and 2,3,7,8-TCDD include thymic atrophy, fatty infiltration of the liver, general edema, delayed head ossification, low birthweight, fetal resorptions, and embryolethality.

Many studies have examined the fetotoxic effects of 2,4,5-T and 2,3,7,8-TCDD on various species. In a study of the effects of 2,3,7,8-TCDD on the rat, no adverse effects were noted at the 0.03 μg/kg level; but fetal mortality, early and late resorptions, and fetal intestinal hemorrhage were observed in groups given 0.125 to 2.0 μg/kg,. the incidence increasing as the dose increased (Sparschu, Dunn, and Rowe 1971). In the CD rat, 2,4,5-T was neither teratogenic nor fetotoxic; however, 2,3,7,8-TCDD produced kidney anomalies (Courtney and Moore 1971). In golden hamsters, 2,4,5-T containing 2,3,7,8-TCDD caused delayed head ossification in a dose-dependent fashion (Collins and Williams 1971). Cystic kidneys occurred unilaterally in 58.9 percent and bilaterally in 36.3 percent of mice pups exposed to 1 μg/kg 2,3,7,8-TCDD (Moore et al. 1973). Murray (1978) reports a three-generation study of rats exposed to 0.001, 0.01, or 0.1 μg/kg of 2,3,7,8-TCDD. Through three successive generations the reproductive capacity of rats ingesting the dioxin was clearly affected at dose levels of 0.01 and 0.1 μg/kg per day, but not at 0.001 μg/kg per day.

In the most recent primate study, eight adult female rhesus monkeys were fed a diet containing 50 ppt 2,3,7,8-TCDD for 20 months (Schantz et al. 1979). After 7 months attempts were made to breed the females. In this group there were four abortions and one stillbirth. All eight control animals reproduced successfully. In the dioxin-exposed group, two animals were not able to conceive and two were able to carry their infants to term.

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*Dilation of renal pelvis usually associated with an obstructed ureter.

One study examined the fetotoxic potentials in mice of other members of the dibenzo-*p*-dioxin class of compounds (Courtney 1976). None of the dibenzo-*p*-dioxins studied were as toxic as 2,3,7,8-TCDD, and some of the compounds could be considered relatively nontoxic. Although the mixture of di-CDD and tri-CDD produced a slight increase in the number of abnormal fetuses, it is doubtful that the malformations were produced by the mixture. Most of the malformations (a mild form of hydronephrosis) were in mouse pups from one litter, and no malformations were observed at a higher dose level. The 1,2,3,4-TCDD compound did not increase the incidence of malformation at any dose level. Oral administration of 5 or 20 mg/kg per day of OCDD to pregnant mice did not alter fetal development. In summary, related dibenzo-*p*-dioxins were relatively nontoxic and were not teratogenic at the doses studied.

CARCINOGENICITY

Several studies of rats and one study of Swiss mice demonstrated an increased incidence of neoplasms in animals exposed to 2,3,7,8-TCDD (Van Miller, Lalich, and Allen 1977; Kociba et al. 1978; Toth et al. 1979). Van Miller and co-workers exposed rats to diets containing the dioxin at concentrations of 1, 5, 50, or 500 ppt, or 1, 5, 50, 500, or 1000 ppb. In this study, the overall incidence of tumors in the experimental groups was 38 percent, with no neoplasms observed in the 1 ppt group. As indicated in Table 44, among the 23 animals with tumors, 5 had two primary neoplastic (cancerous) lesions. Ingestion by rats of 0.1 μg/kg per day 2,3,7,8-TCDD for two years caused an increased incidence of hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate/nasal turbinates, or tongue, and a reduced incidence of tumors of the pituitary, uterus, mammary glands, pancreas, and adrenal glands (Kociba et al. 1978). Figures 61 and 62 illustrate the morphology of some of these lesions. In a recent study with Swiss mice, Toth et al. (1979) showed that 2,4,5-trichlorophenoxyethanol and 2,3,7,8-TCDD enhanced liver tumors in male mice in a dose-dependent fashion. In this study, the increase in liver tumors was statistically significant only at 2,3,7,8-TCDD doses greater than 0.112 μg/kg.

Multiple studies have examined the effects of 2,3,7,8-TCDD administered in combination with other known carcinogens in experimental animal test systems. Two studies used the two-stage tumorigenesis assay of mouse skin (Digiovanni et al. 1977; Berry et al. 1978). Berry and co-workers noted that a dose of 0.1 μg 2,3,7,8-TCDD twice weekly was not sufficient to promote skin tumors in mice treated with 7,12-dimethylbenz(a) anthracene (DMBA). Digiovanni found that at doses of 2 μg per mouse given concurrently with DMBA, the number of tumors observed increased slightly. These data suggest that 2,3,7,8-TCDD is a weak tumor initiator in the two-stage system of mouse skin tumorigenesis. In a more recent study, Digiovanni et al. (1979) found that 2,3,7,8-TCDD could strongly inhibit the initiation of skin tumors by DMBA in female CD-1 mice. In a study with mice that were genetically nonresponsive to the known carcinogen, 3-methylcholanthrene (MCA), exposure to 2,3,7,8-TCDD markedly increased the carcinogenic index of MCA when the compounds were administered simultaneously (Kouri et al. 1978). These data imply that the dioxin could act as a potent cocarcinogen.

GENOTOXICITY

Only four of the dibenzo-*p*-dioxins have been subjected to genotoxicity testing. These are unsubstituted dibenzo-*p*-dioxin, the 2,7-dichloro-isomer, 2,3,7,8-

TCDD, and OCDD (Wassom, Huff, and Loprieno 1978). As expected, 2,3,7,8-TCDD has been the most extensively tested, but results of these studies are inconclusive. Information implicating 2,3,7,8-TCDD as a mutagen is scarce and conflicting. Mammalian studies with dibenzo-*p*-dioxin derivatives have been infrequent. To date, 2,3,7,8-TCDD has shown negative results when tested for dominant lethal effects in rats and weakly positive results when tested for the ability to produce chromosomal abberations in bone marrow cells of rats (Khera and Ruddick 1973; Green, Moreland, and Sheu 1977).

TABLE 44. SUMMARY OF NEOPLASTIC ALTERATIONS OBSERVED IN RATS FED SUBACUTE LEVELS OF 2,3,7,8-TCDD FOR 78 WEEKS[a]

Level of 2,3,7,8-TCDD	No. of animals with neoplasms[b]	No. of neoplasms	Diagnosis
0	0	0	
1 ppt[c]	0	0	
5 ppt	5	6	1 ear duct carcinoma 1 lymphocytic leukemia 1 adenocarcinoma (kidney) 1 malignant histiocytoma (peritoneal)[d] 1 angiosarcoma (skin) 1 Leydig cell adenoma (testes)
50 ppt	3	3	1 fibrosarcoma (muscle) 1 squamous cell tumor (skin) 1 astrocytoma (brain)
500 ppt	4	4	1 fibroma (striated muscle) 1 carcinoma (skin) 1 adenocarcinoma (kidney) 1 sclerosing seminoma (testes)
1 ppb[e]	4	5	1 cholangiocarcinoma (liver) 1 angiosarcoma (skin) 1 glioblastoma (brain) 2 malignant histiocytomas (peritoneal)[d]
5 ppb	7	10	4 squamous cell tumors (lung) 4 neoplastic nodules (liver) 2 cholangiocarcinomas (liver)

a—Source: Van Miller, Lalich, and Allen 1977.
b—10 animals per group.
c—1 ppt = 10^{-12}g 2,3,7,8-TCDD/g food.
d—Metastases observed.
e—1 ppb = 10^{-9}g 2,3,7,8-TCDD/g food.

Mutagenicity

Table 45 summarizes the results of studies of the mutagenic effects of dioxins. None of the *Salmonella* strains capable of detecting base-pair substitutions were positive when tested with 2,3,7,8-TCDD. Some investigations have obtained positive responses in Strain TA 1532, which detects frameshift mutations.

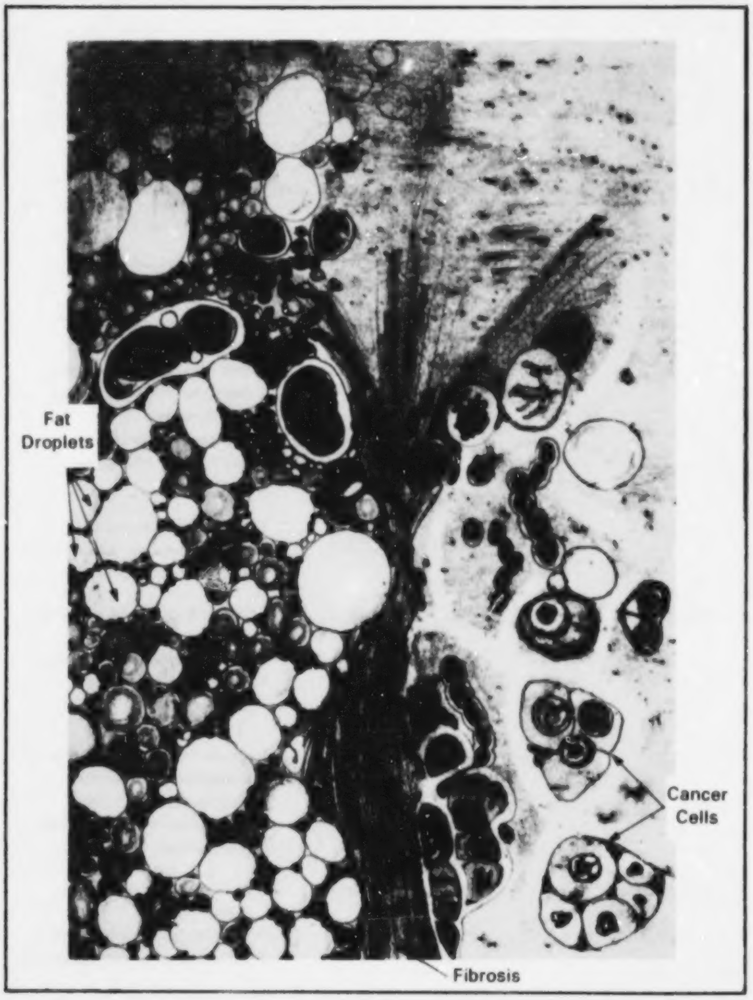

Figure 61. Lesion classified morphologically as hepatocellular carcinoma in liver of rat given 0.1 μg of 2,3,7,8-TCDD/kg per day. Note adjacent fibrosis, inflammation, and fatty infiltration on left. H & E stain. X200.

Source: Redrawn from Kociba et al. 1978.

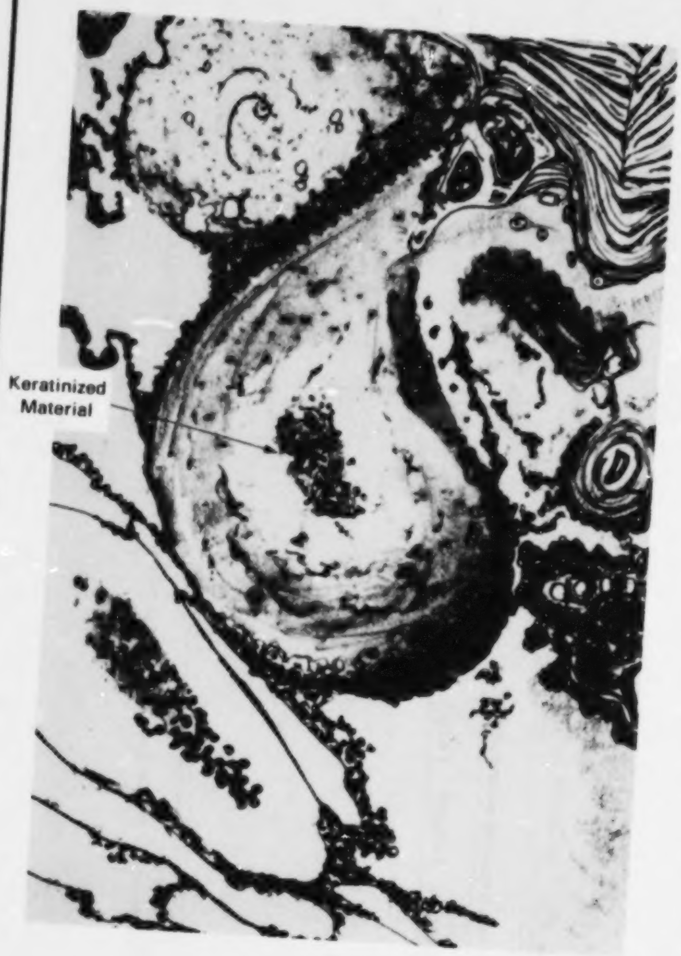

Figure 62. Lesion within lung of rat given 0.1 μg of 2,3,7,8-TCDD/kg per day. Classified morphologically as squamous cell carcinoma. Note accumulation of keratinized material within lesion. H & E stain. X100.

Source: Redrawn from Kociba et al. 1978.

TABLE 45. MUTAGENICITY OF DIOXIN COMPOUNDS IN *SALMONELLA TYPHIMURIUM*[a]

	Strains detecting base-pair substitutions[b]				Strains detecting frameshifts[b]					
Dioxin isomer	**G46**	**TA1530**	**TA1535**	**TA100**	**TA1531**	**TA1532**	**TA1534**	**TA1537**	**TA1538**	**Reference**
2,3,7,8-TCDD	o	o	–	o	o	–	o	–	–	McCann 1975
	o	o	–	o	o	o	o	o	–	Nebert 1976
	o	–	o	o	o	+	o	o	o	Hussain 1972
	–	–	o	o	?	+	?	o	o	Seiler 1973
OCDD	–	–	o	o	–	?	?	o	o	Seiler 1973
Dibenzo-*p*-dioxin	o	o	–	–	o	o	o	–	–	Commoner 1976

a—Source: Wassom, Huff, and Loprieno 1978.

b—Key: o = not tested; – = negative results; + = positive results; ? = doubtful mutagen. Results obtained with different experimental protocols.

Hussain et al. (1972) report the following results of mutagenicity studies with 2,3,7,8-TCDD (99 percent) on three bacterial systems:

1. 2,3,7,8-TCDD significantly increased the incidence of reverse mutations from streptomycin-dependence to streptomycin-independence in the bacteria *Escherichia coli* SD-4 treated with 2 μg/ml 2,3,7,8-TCDD. This was the only concentration at which mutations were clearly observed.
2. Evaluation of reverse mutation from histidine-dependence to histidine-independence in *Salmonella typhimurium* strains TA 1532 and TA 1530 indicated that 2,3,7,8-TCDD was positive in TA 1532 but negative in TA 1530. This finding indicates that the dioxin may act as a frameshift mutagen. ICR-170 was used as a positive control in the test with 1532, but no positive or negative controls were tested with TA 1530
3. Slight prophage inductions in *Escherichia coli* K-39 were observed, although data were difficult to evaluate because the DMSO solvent used in this test caused cellular effects on its own.

Seiler (1973) studied the effects of 2,3,7,8-TCDD and OCDD in several strains of *Salmonella typhimurium*. The 2,3,7,8-TCDD was strongly mutagenic only in strain TA 1532, whereas the OCDD was questionably mutagenic in strains TA 1532 and TA 1534. McCann (1976) obtained no positive mutagenic responses in several *Salmonella* strains exposed to 2,3,7,8-TCDD, including TA 1532. Commoner (1976) demonstrated that unsubstituted dibenzo-*p*-dioxin was nonmutagenic in four strains of *Salmonella typhimurium*.

Khera and Ruddick (1973) performed dominant lethal studies with 2,3,7,8-TCDD. Groups of male Wistar rats were dosed orally with 4, 8, or 12 μg/kg per day for 7 days before they mated. Although the incidence of pregnancies from all matings was reduced, there was no evidence of induction of dominant lethal mutations during postmeiotic phases of spermatogenesis.

Cytotoxicity

Highly purified samples of 2,4,5-T and 2,3,7,8-TCDD were evaluated for cytological effects in the African Blood Lily plant (Jackson 1972). The tests included treatments involving both compounds in varying proportions. In contrast to a no-effect result with a highly purified sample of 2,4,5-T, dramatic inhibition of mitosis was observed in cells exposed either to a 10^{-4} molar solution of 2,4,5-T containing 0.2 to 1.0 μg 2,3,7,8-TCDD per liter or to a 10^{-4} molar solution of 2,4,5-T containing an unknown level of 2,3,7,8-TCDD. Similar results were obtained when treatments were limited to 2,3,7,8-TCDD alone. These treatments also induced formation of dicentric bridges and chromatin fusion, with formation of multinuclei or a single large nucleus. Because these effects were not evident in the pure 2,4,5-T sample, Jackson concluded that the cytological effects were due to the 2,3,7,8-TCDD contaminant.

Tests for cytological effects in a wild type *Drosophila* fly were conducted with 2,4,5-T containing less than 0.1 ppm 2,3,7,8-TCDD (Davring and Summer 1971). Twenty-four hours after eclosion the adult flies were exposed to 250 ppm 2,4,5-T in their food. Results indicated that this formulation affected early oogenesis and caused sterility. It is not stated unequivocally that the observed sterility was of genetic origin.

In an animal study (Greig et al. 1973), male Portion rats were treated with single oral doses (50 to 400 μg/kg) of 2,3,7,8-TCDD dissolved in either dimethyl sulfoxide or arachis (peanut) oil. In the rat livers, parenchymal cell structures were altered and many cells were multinucleated. No mitoses were observed, and there were occasional pyknotic nuclei. The investigators postulate that 2,3,7,8-TCDD interfered with the capacity of the liver cells to maintain their correct morphology and thus led to death or structural disorganization. Similar results have been obtained by others (Buu-Hoi et al. 1971; Kimbrough et al. 1977). Vos et al. (1974) suggest that 2,3,7,8-TCDD could be a hepatocarcinogen because of its specific cytological effects on the proliferating cells of the liver.

Chromosomal abberations in bone marrow cells of 2,3,7,8-TCDD-treated Osborne-Mendel rats have also been reported (Green, Moreland, and Sheu 1977). No chromosomal abberations or cytogenetic damage was found, however, in bone marrow of male Osborne-Mendel rats treated with 2,7-di-CDD or unsubstituted dibenzo-*p*-dioxin (Green and Moreland 1975).

2,3,7,8-TCDD may be mutagenic to humans. Chromosomal abnormalities have been reported in in vitro cytogenetic studies of human lymphocytes exposed to 10^{-7} to 10^{-4}m-molar solutions of 2,4,5-T that contained 0.09 ppm 2,3,7,8-TCDD (U.S. EPA 1978h). Breaks, deletions, and rings were observed. Chromatid breaks increased with increasing concentrations of 2,4,5-T. It was not possible to distinguish whether this was a toxic effect or a potential genetic effect.

Pathophysiology

Many investigators have tested apparently logical mechanisms of action for 2,3,7,8-TCDD toxicity. For the most part, these investigations have served only to disprove proposed mechanisms of action (Beatty et al. 1978; Neal 1979). The following proposed mechanisms for toxicity induced by 2,3,7,8-TCDD have been disproved:

- Inhibition of protein synthesis
- Inhibition of DNA synthesis
- Inhibition of mitosis
- Inhibition of oxidative phosphorylation
- Interference with the action of thyroxine
- Interference with glucocorticoid metabolism
- Increased serum ammonia levels
- Depletion of reduced pyridine nucleotides
- Production of superoxide anion
- Decreased hepatic ATP content
- Impairment of hepatic mitochondrial respiration

The most promising explanations for at least the first step in the mechanism of 2,3,7,8-TCDD toxicity result from studies of hepatic ATPase activities (Jones 1975; Madhukar et al. 1979b). Jones administered 200 μg/kg of the dioxin to male albino rats, then sacrificed groups of animals at 24 hours and at 3, 5, 6, 8, 34, and 42 days. Hematoxylin and eosin stains of liver sections showed no abnormalities in the groups sacrificed in the 24-hour to 8-day intervals; however, in the remaining two groups (34 and 42 days) the liver sections showed centrilobular zone necrosis. As early as 3 days after exposure, a significant change in the pattern of the ATPase reaction was seen in all animals studied. In an area five to six cells deep around the central vein, there was no reaction along the canalicular borders of the parenchymal cells. Similar results were obtained by Madhukar, who studied Na-, K-, and Mg-ATPase activities in hepatocyte surface membranes isolated from male rats given 10 or 25 mg/kg 2,3,7,8-TCDD. As early as 2 days after administration of the dioxin, all of the ATPase activities were depressed in treated animals. A dose-response relationship was observed only for depression of Mg-ATPase activity. In further studies, Madhukar demonstrated that ATPase depression was not produced by in vitro exposures to 2,3,7,8-TCDD.

EPIDEMIOLOGICAL STUDIES AND CASE REPORTS

The most notable human exposures to 2,3,7,8 tetrachlorodibenzo-*p*-dioxin have occurred through accidental releases in chemical factories, or by exposure to contaminated materials or areas. Most of the studies reported in the literature, such as those cited below, are investigations of the effects of such exposures.

General Acute Toxicity

The immediate results of dioxin exposure are burning sensations in eyes, nose, and throat; headache; dizziness; and nausea and vomiting (U.S. NIEHS IARC 1978). Itching, swelling, and redness of the face may occur just prior to chloracne. Chloracne, similar to acne vulgaris, is one of the most consistent and prominent features of dioxin exposure, occurring within weeks of initial exposure (May 1973; Oliver 1975; Poland et al. 1971). McInty (1976) showed that as little as 20 μg of 2,3,7,8-TCDD on the skin can lead to chloracne development. Chloracne may appear fist on the face and then spread to the arms, neck, and trunk (U.S. NIEHS IARC 1978; May 1973). Other symptoms of exposure include arthralgias (pains in the joints without associated arthritic changes), extreme fatigue, insomnia, loss of libido, irritability, and nervousness (Ensign and Uhi 1978; U.S. NIEHS IARC 1978). High levels of blood cholesterol and hyperlipoproteinaemia may also develop (Oliver 1975).

Other effects, which may be delayed or immediate, are porphyria cutanea tarda, hepatic dysfunction, hyperpigmentation, and hirsutism (U.S. NIEHS IARC 1978). Disorders of the cardiovascular, urinary, respiratory, and pancreatic systems (Goldman 1973), along with disorders of fat and carbohydrate metabolism also have been found (U.S. NIEHS IARC 1978). Emotional disorders, difficulties with muscular and mental coordination, blurred vision, and loss of taste and smell also may occur (Oliver 1975).

Several deaths related to 2,3,7,8-TCDD have been recorded, some due to liver damage and others to chronic exposure to the chemical. Additionally, symptoms such as chloracne can be passed by an exposed person to close associates such as family members through clothing, hands, or other close contact (McInty 1976).

General Chronic Toxicity

Poland et al. (1971) studied possible toxic effects on 73 male workers in a factory producing the 2,3,7,8-TCDD-contaminated pesticide 2,4,5-T. The workers were classified according to job location. The medical or toxicological symptoms were grouped into three categories: 1) chloracne and mucous membrane irritation, 2) hepatotoxicity, neuromuscular symptoms, psychological alterations, and other systemic symptoms, and 3) porphyria cutanea tarda (PCT). Of the 73 subjects, 66 percent experienced some degree of chloracne, 18 percent of which was classed as moderate to severe. The presence of hyperpigmentation and hirsutism correlated with the severity of the acne. Among maintenance men, who were subject to the greatest exposure, the acne was more severe than that of administrative personnel, whose exposure was minimal. Urinary porphyrin values, although within normal limits, were elevated in the maintenance men as compared with the other workers. Although 2,3,7,8-TCDD and other chemicals produced in 2,4,5-T synthesis may be hepatotoxic in humans, demonstrable chemical liver dysfunction among workers in this plant was minimal.

The toxic effect of 2,3,7,8-TCDD on three young laboratory scientists was reviewed in a case study by Oliver (1975). Two of the subjects worked with the dioxin for approximately 6 to 8 weeks, and the third for approximately 3 years before onset of symptoms. The latter scientist worked only with a diluted sample of the material, whereas the other two worked on the synthesis of dioxins. Chloracne was the first symptom experienced by two of the scientists. Two of them also suffered from delayed reactions, experiencing abdominal pain, headache, excessive fatigue, uncharacteristic episodes of anger, diminished concentration, other neurological disturbances, and hirsutism approximately 2.5 years after exposure. None of the scientists showed liver damage or porphyrinuria; all three showed elevated serum cholesterol levels, evidence of hypocholesterolemia, and hyperlipoproteinaemia. No other biochemical abnormalities were noted. Over a period of 6 months (after the onset of the delayed symptoms), the symptoms subsided. All three scientists were aware of the danger involved in the substance with which they were working; they wore protective clothing, gloves, and masks, and worked under a vented hood. The author speculated that the exposures must have been extremely low.

Accidental release of 2,3,7,8-TCDD occurred in an explosion at a chemical plant in Derbyshire, England. This exposure of workers resulted in 79 cases of chloracne recorded approximately 3 weeks after the explosion (May 1973). Young men with fair complexions were affected first, but the symptoms persisted longer in sallow-skinned men ages 25 to 40. Chloracne was present, in order of prevalence, on the face, extensor aspects of arms, lateral aspects of thighs and calves, back, and sternum. Most workers recovered in 4 to 6 months. Of 14 employees who were present during the explosion, 13 showed abnormal liver function and 9 developed chloracne. Those with chloracne had handled pipes, joints, and cables with bare hands and thus may have absorbed the dioxin through the skin; this finding suggests that excretion of absorbed dioxin or its products may occur through facial pores.

Jirasek et al. (1973, 1974, 1976) cite many studies done on 80 industrial workers in Czechoslovakia who showed signs of intoxication from dioxin formed as a byproduct in production of the sodium salts of 2,4,5-T and pentachlorophenol. Symptoms included 76 cases of chloracne, ranging from mild to so severe that it covered the entire body and left scars. Twelve workers had hepatic lesions with symptoms of porphyria cutanea tarda. Symptoms in 17 of the workers included polyneuropathy, psychic disorders, weakness and pain in the lower extremities, somnolence or insomnia, excessive perspiration, headache, and disorders of the mental and sexual functions. One worker suffered and died from severe atherosclerosis, hypertension, and diabetes; two workers died from bronchogenic carcinoma (lung cancer) (ages 47 and 59). Periods of latency differed; in some instances severe dermatological and internal damage developed after brief exposure, whereas in others apparently long-term and massive exposure caused only mild symptoms.

Another study (Poland and Kende 1976) deals with 29 workers who were accidentally exposed to 2,3,7,8-TCDD. Of the 29, all contracted chloracne, 11 developed porphyrinuria, and several developed porphyria cutanea tarda. The workers also showed signs of mechanical fragility, hyperpigmentation, hirsutism, and photosensitivity of the skin, in which sunlight exposure caused blistering. Measures were taken at this plant to decrease 2,3,7,8-TCDD production and worker exposure. Within 5 years there was no evidence of porphyria or severe acne, and severity of the other symptoms was also reduced. In all cases reviewed, an acute exposure to dioxins resulting in chloracne and other acute symptoms and followed by a period of nonexposure to the substance resulted in the disappearance or diminution of the symptoms.

In early May of 1971, an accidental poisoning incident killed or intoxicated many horses and other animals that came in contact with the soil of an arena sprayed with contaminated oil. Investigators identified 2,3,7,8-TCDD and polychlorinated biphenyls as the causative agents (Carter et al. 1975; Kimbrough et al. 1977). A six-year old girl who played in the arena soil developed symptoms of headache, epistaxis (nosebleed), diarrhea, and lethargy. In August 1971, she developed hemorrhagic cystitis (inflammation of the urinary bladder). The patient's symptoms resolved in 3 to 4 days and did not recur. Proteinuria and hematuria (protein and blood in the urine) disappeared within 1 week of onset. A voiding cystogram obtained 3 months later appeared normal; however, cystoscopy demonstrated numerous punctate hemorrhagic areas, especially in the trigone region of the bladder. The patient was reexamined 5.3 years after dioxin exposure. Physical examination was performed, as well as urinalysis, a voiding cystogram, an intravenous pyelogram, renal function chemistries, an electrocardiogram, stress test, liver-function tests, uroporphyrin excretion, and thyroid-function studies. Results of all tests were essentially within normal limits (Beale et al. 1977). Three other individuals exposed to the arena developed recurrent headaches, skin lesions, and polyarthralgia (Kimbrough et al. 1977).

In another sprayed arena, two three-year-old boys developed small, pale, nonpruritic, firm papules covered by blackheads on the exposed skin surfaces. These symptoms arose 1.5 months after the spraying. They increased in severity and lasted more than a year before gradually subsiding (Carter et al. 1975).

Perhaps the most publicized incident of dioxin poisoning was that in Seveso, Italy. On July 10, 1976, at a plant where trichlorophenol was manufactured, an accident created temperature conditions ideal for formation of 2,3,7,8-TCDD (Zedda, Circla, and Sala 1976). Trichlorophenol crystals and 2,3,7,8-TCDD in the form of dust were spread over the area (Hay 1976a). In addition to 170 plant employees, approximately 5000 persons were exposed (Zedda, Circla, and Sala 1976).

Shortly after the accident, cases of chloracne were reported. Over the ensuing years more than 134 confirmed cases of chloracne have occurred in children, some of whom had not been in the area during July and August 1976. These latter cases indicate that enough dioxin persisted in the environment several months after the accident to cause the chloracne (Zedda, Circla, and Sala 1976). Reports of disorders among the 170 workers exposed include 12 cases of chloracne in directly contaminated workers, 29 cases of hepatic insufficiency, 28 cases of chronic bronchitis, 17 cases of arterial hypertension, 9 cases of coronary insufficiency, 8 cases of muscular asthenia (weakness), and 3 cases of reduced libido (Zedda, Circla, and Sala 1976). Reported symptoms occurring among the exposed residents include chloracne, nervousness, changes of character and mood, irritability, and loss of appetite. Legal and illegal abortions were estimated at 90, and there were 51 spontaneous abortions (U.S. EPA 1978h).

Several additional followup studies of the initially identified cohort have been reported recently (Reggiani 1978, 1979a,b; Pocchiari, Silano, and Zampieri 1979). In 1978, Reggiani reported that chloracne had appeared almost only in children and young people. These cases tended to be mild, and spontaneous healing occurred in most. Transient lymphocytopenia and liver function abnormalities were detected. Reports at that time indicated no overt pathology of the liver, kidney, blood, reproductive organs, central and peripheral nervous systems, or metabolism of carbohydrate, fat or porphyrin. In 1979, Reggiani reported that the incidence of chloracne remained between 0.6 and 1.5 percent in the surveyed population and other toxic manifestations initially observed remained at subclinical levels.

Pocchiari, Silano, and Zampieri (1979) reported a somewhat more detailed followup of the cohort. In the cohort with highest exposure, chloracne was identified in approximately 13 percent of the screened population. About 4 percent of the workers from the plant (Pocchiari sets the number at 200) showed signs and symptoms of polyneuropathy. Subclinical peripheral nerve damage, confirmed by nerve conduction studies, was also observed fairly frequently in nonoccupationally exposed groups, and the incidence ranged from 1.2 to 4.9 percent in the screened population. Of note, there were no documented immunologic alterations in the exposed population. Eight percent of the screened population showed hepatomegaly of undetermined etiology, and some of the screened population showed elevated levels of liver transaminases.

The long-term effects of exposure to 2,3,7,8-TCDD in Seveso are not clear at this time. An epidemiologic survey now in progress includes general and specialized medical examinations, laboratory tests, and data on the outcome of pregnancies. Data will be collected over a period of 5 years. Cancer registries, hospital discharge forms, notifications of infectious diseases, and birth and death certificates will be used to detect any abnormalities of the health of the community (Fara 1977).

Fetotoxicity and Teratogenicity

Hexachlorophene (HCP) is a derivative of 2,4,5-TCP that has been used as an antibacterial agent for the past 20 years. Although there are no reports of 2,3,7,8-TCDD contamination in HCP, this drug has been shown to cause fetal malformations, some of which are severe (U.S. NIEHS IARC 1978). A study of mothers who were nurses exposed to hexachlorophene soap during early pregnancy showed that of 65 children born, 5 had severe and 6 had slight malformations. One slight malformation was observed in 68 children of an unexposed control group. Five babies died who had been washed more than three times with 3 percent hexachlorophene in a hospital. Autopsies revealed considerable brain damage in each case. In 1972, many infant fatalities were reported in France. The cause was cited as a new talc powder called "Bebe," which contained 6 percent HCP (dioxin content, if any, is unknown) (McInty 1976).

It is reported that the local spontaneous abortion rate has increased to twice the national level in Italy since the chemical contamination of Seveso in 1976, and that similar results have occurred in Vietnam since the spraying of Herbicide Orange (Nature 1970). Unfortunately, doctors in Vietnam are unable to document increased abortion and birth defects because of inadequate medical records (U.S. EPA 1978a).

In the sprayed areas of Vietnam, doctors have cited increased incidences of babies being born with extra fingers or without fingers, hands, or feet (Lawrence Eagle Tribune 1978). Recently, a group of U.S. military veterans who were in South Vietnam at the time of the spraying have reported birth defects in their offspring similar to those reported in South Vietnam (Ensign and Uhi 1978; Lawrence Eagle Tribune 1978; Peracchio 1979).

An EPA study has been done on the relationship of dioxin-containing herbicides to miscarriages; specifically the study concerns the relationship between spraying 2,4,5-T on forested areas of Oregon and miscarriages among women living in Alsea, a town near a sprayed area. Scientists from Colorado State University and the University of Miami medical school compared miscarriages in the Alsea basin with those in a control area in rural eastern Oregon. The miscarriage rate in the Alsea area was significantly higher than in the control area, where 2,4,5-T was not sprayed. Miscarriage rates peaked dramatically in June of each of the 6 years studied, occurring 2 or 3 months after the yearly spring applications. From 1972 through 1977 the spontaneous abortion indexes in June were 130 per 1000 births in Alsea and 46 per 1000 in the control area. Although these data do not prove a cause and effect relationship, they are highly suggestive (Cookson 1979).

A recent study deals with the relationship of neural-tube defects in New South Wales and annual usage rates of 2,4,5-T in the whole of Australia (Field and Kerr 1979). Table 46 gives data showing the annual New South Wales combined birth rates of anencephaly (congenital absence of the cranial vault), and meningomyelocele (defect through which part of the spinal cord communicates with the environment), together with data on the usage of 2,4,5-T in Australia in the previous year. The plot in Figure 63 indicates linear correlation. Highest rates on neural-tube defects occurred for conceptions during the summer months, and maximum spraying of 2,4,5-T in New South Wales occurs during the summer months. Again, although these data are suggestive, they do not prove a cause and effect relationship. The linear correlation disappeared in 1975 and 1976;

TABLE 46. COMBINED RATE OF NEURAL-TUBE DEFECTS IN NEW SOUTH WALES AND PREVIOUS-YEAR USAGE OF 2,4,5-T IN AUSTRALIA[a]

Year	Neural-tube defects in New South Wales (cases per 1000 births)	Usage of 2,4,5-T in Australia in previous year (metric tons)[b]
1965	1.72	90
1966	1.77	105
1967	1.93	188
1968	1.83	213
1969	2.13	201
1970	2.37	282
1971	1.88	170
1972	2.15	256
1973	2.19	241
1974	2.27	287
1975	2.03	466
1976	2.30	482

a—Source: Field and Kerr 1979.
b—2,4,5-T acid in equivalent metric tons.

monitoring of 2,4,5-T herbicide was established in Australia to ensure that concentrations of 2,3,7,8-TCDD remain below 0.1 ppm.

Nelson et al. (1979) report a retrospective study of the relationship between use of 2,4,5-T in Arkansas and the concurrent incidence of facial clefts in children. Occurrences of facial cleft generally increased with time; however, no significant differences were found in any of the study groups. The authors conclude that the general increase in facial cleft incidence in the high- and low-exposure groups resulted from better case finding rather than from maternal exposure to 2,4,5-T.

Among 182 babies delivered in Seveso in the 2 months after the accident, only 16 birth anomalies were found. This level is not significantly higher than the national level. Women in early stages of pregnancy when the accident happened were not studied in this survey (U.S. EPA 1978a).

Carcinogenicity

Ton That et al. (1973) report an increase in the proportion of primary liver cancer among all cancer patients admitted to Hanoi hospitals during the period 1962 to 1968; this increase is relative to the period 1955 to 1961, just before the spraying of Herbicide Orange began.

Theiss and Goldmann (1977) trace 4 cancer deaths out of 15 deaths occurring in 53 workers exposed to 2,3,7,8-TCDD after a manufacturing accident in a TCP plant in Ludwigshafer, Germany, in 1953. A followup study is in progress.

Two studies show an increased incidence of malignant mesenchymal soft-tissue tumors in persons exposed to phenoxy acids or chlorophenols (Hardell and Sandstrom 1978; Hardell 1979). In the 1978 study, 52 patients with soft-tissue sarcomas and 205 matched controls were investigated in a cohort study. The incidence of exposure was 19/52 among the tumor patients and 19/206 in the tumor-free controls ($p < 0.001$). Relative risks were determined to be 5.3 for

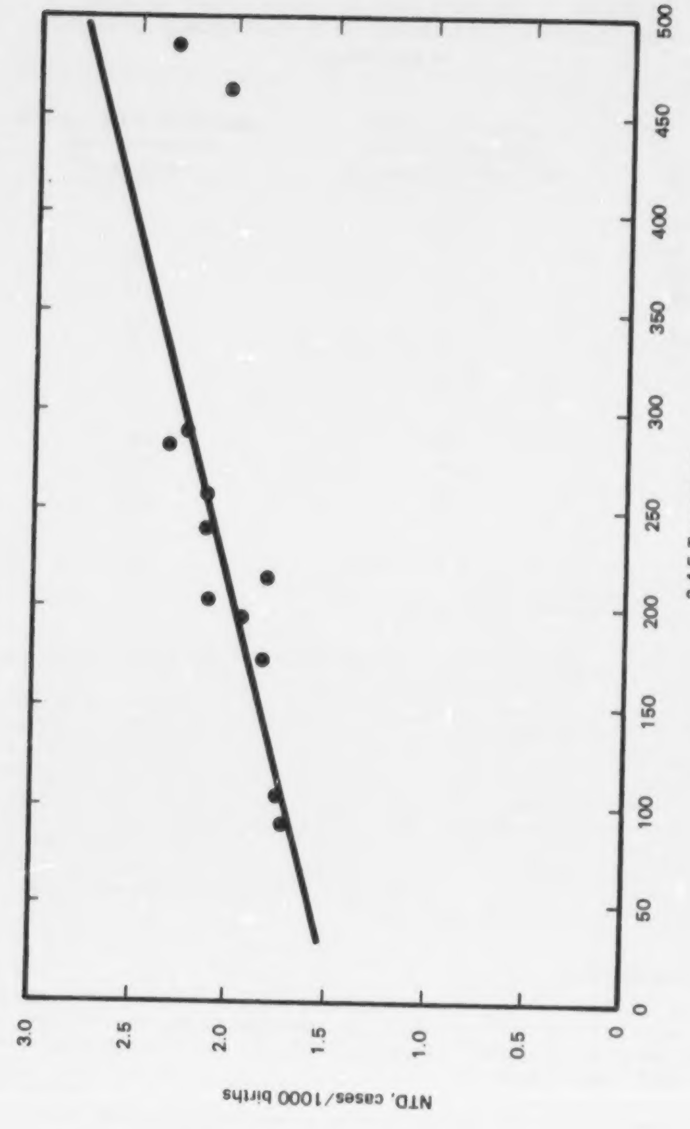

Figure 63. Linear correlation of New South Wales rate for neural-tube defects with previous year's usage of 2,4,5-T in Australia.

Source: Field and Kerr 1979.

exposure to phenoxy acid and 6.6 for exposure to chlorophenols. In the 1979 study, Hardell prospectively studied patients with histocytic, malignant lymphoma. In the first phase of the study, 14 of 17 patients reported occupations consistent with the possibility of exposure to the chemicals under study, and 11 patients reported definite exposure to phenoxyacetic acids or chlorophenols. The median latent period between exposure and tumor detection in this group was 15 years.

Rappe (1979) has reported an increased incidence of primary liver cancer in members of the Vietnamese population exposed to Herbicide Orange.

Mutagenicity

Chromosomal analyses in Seveso have shown an increase in chromosomal lesions in males and females aged 2 to 28 years. These lesions consist of chromosomal gaps, and chromatid and chromosomal breaks and rearrangements. Cytogenetic studies indicate chromosomal damage to cells in maternal peripheral blood and in placental and fetal tissues studied following therapeutic abortions (U.S. EPA 1978h).

In similar analyses, Tenchini et al. (1977) found a higher number of structural aberrations in the fetal tissues than in the maternal blood samples of fibroblast cells from adult tissues, but the frequency of these aberrations did not appear to be greater than expected to occur spontaneously in cultures of comparable cell types. Tenchini et al. point out that these preliminary findings do not indicate whether the higher frequencies of chromosome aberrations in fetal tissues were due to chromosome damage caused by 2,3,7,8-TCDD exposure.

In contrast, the chromosomes of peripheral blood cells from 90 workers at the chemical plant at Seveso showed no abnormalities; the same results were obtained in a sampling of the most severely exposed residents of the area (Wassom 1978).

Czeizel and Kiraly (1976) compared the frequency of chromosome aberrations in the peripheral lymphocytes of 76 workers employed at a herbicide-producing factory in Budapest with those of 33 controls. Among these workers, 36 were exposed to 2,4,5-trichlorophenoxyethanol (TCPE) or Klorinol and 26 to Buvinol. The remaining 14 workers had never been engaged in the production or use of either herbicide. The 2,3,7,8-TCDD concentration in the herbicide products is reported to be either less than 0.1 mg/kg or not more than 0.05 mg/kg. The frequency of chromatid-type and unstable chromosome aberrations was higher ($p < 0.01$) in the factory workers than in the controls, regardless of involvement in production of the herbicide. Aberrations were more frequent in workers preparing TCPE and Buvinol than in other factory workers, but the difference was significant only for the chromatid-type effect.

SECTION 7

ENVIRONMENTAL DEGRADATION AND TRANSPORT

This section addresses the fate of dioxins once they are released to the environment. Subsections on biodegradation and photodegradation deal with recent literature relating to biochemical and physical actions of the environment as they affect the integrity of the dioxin structure. Subsections on physical and biological transport deal with the movement of dioxins in soil, water, and air and with the uptake of dioxins by plants and their fate in animals at various trophic levels.

BIODEGRADATION

In assessment of the persistence of a substance in the environment, the susceptibility of that substance to biodegradation* is a primary concern. Several studies on the biodegradability** of dioxins are described in the literature. The investigations show that dioxins exhibit relatively strong resistance to biodegradation, though they may not necessarily be totally recalcitrant. Most of the work has focused on 2,3,7,8-TCDD because of its extreme toxicity. This dioxin has been studied in both aqueous and soil environments, and results have been somewhat equivocal. Only one study (Kearney et al. 1973) has examined the biodegradability of another dioxin, 2,7-DCDD. Data from this study indicate that this dioxin can be at least partially degraded in soils. Several dioxin biodegradation studies are described in the following paragraphs, but due to recent information concerning problems of extracting dioxins from the test soils, it must now be concluded that the biodegradability of dioxins has not been demonstrated.

Approximately 100 strains of microbes that had previously shown the ability to degrade persistent pesticides were tested for their ability to degrade 2,3,7,8-TCDD. After incubation, extracts from microorganisms were prepared and analyzed for metabolites by thin-layer chromatography. Of the strains tested, five showed some ability to degrade the dioxin.

Some studies, as described in the next three paragraphs and other places within this compilation, have been conducted with ^{14}C-labeled 2,3,7,8-TCDD. Dow Chemical Company points out that ^{14}C-labeled experiments are limit-producing only and are not quantitative in spite of some data being reportd to two significant figures (Crummett 1980).

Ward and Matsumura studied the biodegradation of ^{14}C-labeled 2,3,7,8-TCDD in Wisconsin lake waters and sediments and reported in 1977 that the dioxin may be genuinely metabolized in aqueous systems, but that the rate is very low. They concluded that there is an optimum time for microbial degradation, probably 1 month, and that during this period, available 2,3,7,8-TCDD is degraded while the nonavailable fraction is bound to the water sediments. The limited degradation of

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*Biodegradation: the molecular degradation of an organic substance resulting from the complex actions of living organisms. A substance is said to be biodegraded to an environmentally acceptable extent when environmentally undesirable properties are lost. Loss of some characteristic function or property of a substance by biodegradation may be referred to as biological transformation. (CEFIC 1978)

**Biodegradability: the ability of an organic substance to undergo biodegradation.

2,3,7,8-TCDD is favored by the presence of sediment, microbial activity, and/or organic matter in the aqueous phase. The observed half-life of 2,3,7,8-TCDD in sediment-containing lake waters was 550 to 590 days; the half life in waters without sediment was longer.

Kearney and co-workers studied two types of soil, which were incubated with 2,3,7,8-TCDD at concentrations of 1, 10, and 100 ppm and with ^{14}C-labeled 2,3,7,8-TCDD at concentrations of 1.78, 3.56, and 17.8 ppm (Kearney et al. 1973a). The two soils were also inoculated with ^{14}C-labeled 2,7-DCDD at concentrations of 0.7, 1.4, and 7.0 ppm. The soil types were Hagerstown silt clay loam, which is relatively high in organic matter and microbial activity, and Lakeland sandy loam, which is low in organic matter and microbial activity. Over a 9- to 10-month period, the soil samples were monitored weekly for evolution of gaseous $^{14}CO_2$ as an indication of microbial degradation of the labeled dioxins.

Very little CO_2 was liberated from soils containing either labeled or unlabeled 2,3,7,8-TCDD. In most cases 75 to 85 percent of the dioxin was recovered from both soil types up to 160 days after addition. No metabolites were found in TCDD-treated soil after 1 year. About 5 percent of the ^{14}C-2,7-DCDD had degraded to liberate $^{14}CO_2$ after 10 weeks. Concentrations of ^{14}C-2,7-DCDD in the soil had a slight effect on $^{14}CO_2$ evolution. It was postulated that the decrease in CO_2 liberation at the highest level may have resulted from the toxicity of the DCDD isomer to the microbes at this concentration. Evolution of $^{14}CO_2$ was significantly higher in the Lakeland soil than in the Hagerstown soil. Analysis of DCDD-treated soil extracts also revealed the presence of metabolites, but the major metabolite could not be identified.

In the same study, incubation of a clay loam (with relatively low organic matter) to which ^{14}C-2,3,7,8-TCDD had been applied led to liberation of a "very small amount of $^{14}CO_2$" after 2 weeks.

The U.S. Air Force studied test plots in Utah, Kansas, and Florida to determine the soil degradation rate of 2,3,7,8-TCDD under field conditions (Young et al. 1976). The three test plots were considered representative of various climatic conditions and soil types. Herbicide Orange containing 3700 ppb 2,3,7,8-TCDD was applied to all three plots at a rate of 4480 kg/hectare. Initial soil concentrations of the dioxin were not reported for any of the sites. Composite samples from the upper 15 cm of each soil were taken from time to time after the initial herbicide application, and analyzed for both the herbicide and 2,3,7,8-TCDD. Results are presented in Table 47.

From these data and other leaching data, the Air Force concluded that the disappearance of 2,3,7,8-TCDD was most likely due to degradation by soil microbes, because dioxin concentrations in the 15- to 30-cm layer indicated that leaching was insignificant. The Air Force report further stated that dioxin degradation was most rapid in the Kansas soil (Ulysses silt loam), followed by the Florida soil (Lakeland sandy loam), and finally the Utah soil (Lacustine clay loam), but that variations in soil and climate had little overall influence on dioxin persistence. It was also reported that the initial breakdown rate was rapid, but decreased substantially over the test period. On the basis of this observation the investigators speculated that microbial enzymes responsible for herbicide metabolism and possibly dioxin metabolism are inducible.

In an evaluation of the Air Force studies, Commoner and Scott (1976) came to different conclusions. After constructing semilogarithmic plots of dioxin concentrations in soil against days after incorporation of the dioxin, they concluded: (1) that there was no evidence that the rate of degradation changed with time; and (2) that degradation appeared to be more rapid in the Florida soil than in the Kansas soil (opposite of the Air Force conclusion).

In another Air Force study with dioxin-contaminated soil the effects of nutrients and mixing on 2,3,7,8-TCDD degradation were assessed (Bartleson, Harrison, and Morgan 1975). Pots containing either test soils or control soils were placed

TABLE 47. CONCENTRATIONS OF HERBICIDE ORANGE AND 2,3,7,8-TCDD IN THREE TREATED TEST PLOTS[a]

Test plot	Days after application	Total herbicide[b] (ppm)	2,3,7,8-TCDD (ppb)
Utah	282	8490	15.0
	637	4000	7.3
	780	2260	5.6
	1000	2370	3.2
	1150	960	2.5
Kansas	8	1950	c
	77	1070	0.255
	189	490	c
	362	210	c
	600	40	c
	659	<1	0.042
Florida	5	4897	0.375
	414	1866	0.250
	513	824	0.075
	707	508	0.046
	834	438	c
	1293	<10	c

a—Plots treated with 4480 kg herbicide per hectare.
b—Composite sample from upper 0 to 15 cm layer of soil.
c—Not analyzed.

outdoors and in a greenhouse. The soils were analyzed after 9 and 23 weeks. Soils tested in the greenhouse were moistened with a nutrient solution. The results are presented in Table 48.

The investigators concluded that the accelerated rate of degradation observed in soil from the pots in the greenhouse during the first 9-week period was probably due to increased microbial populations resulting from initial soil aeration and increased soil temperatures in the pots. Reduction in the rate of breakdown after 9 weeks may have been caused by leaching or entrapment of dioxin in the bottom soil layer, which had not been mixed. It was also proposed, however, that the nutrient solution together with light or aeration caused either a direct chemical breakdown of 2,3,7,8-TCDD in the soil or an increase in microbial populations that accelerated breakdown. Because green algae were observed on the surface of the greenhouse pots between tillings, it was also postulated that the algae were partly responsible for the degradation.

This study was also evaluated by Commoner and Scott (1976), who concluded that mixing, nutrients, and increased exposure to sunlight did not significantly enhance degradation of 2,3,7,8-TCDD in soil.

Pocchiari (1978) attempted to stimulate the microbial degradation of 2,3,7,8-TCDD in samples of Seveso soil contaminated with the dioxin from the 1976 ICMESA accident. The dioxin-contaminated soil samples were either inoculated with promising microorganisms (according to the previously described results of Matsumura and Benezet in 1973) or enriched by the addition of organic nutrients. No positive degradation effects have been found.

TABLE 48. DEGRADATION OF 2,3,7,8-TCDD IN SOIL[a]
(parts per trillion 2,3,7,8-TCDD)

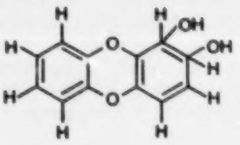
	Length of exposure (weeks)		
	0	9	23
Controls	1100–1300		
Outdoor exposure			
Tilled (top layer)		1100	520
Untilled		1000	530
Greenhouse			
Tilled (top layer)		640	460
Untilled		810	530

a—Source: Bartleson, Harrison, and Morgan 1975.

Investigators from the Microbiological Institute in Zurich, Switzerland, have found that microbes cannot contribute quickly or efficiently to the decontamination of soil-bound 2,3,7,8-TCDD, although they might contribute slowly (Huetter 1980). The latter point is supported by the observation of two polar bands in thin-layer chromatographs of some microbial incubations. Huetter and co-workers also have observed that when 2,3,7,8-TCDD is incubated with soil for a prolonged period of time, it is not as extractable as when it is freshly added to the soil, indicating that recoverability of the dioxin becomes increasingly more difficult with time. This information raises questions about the accuracy of work done by others in the past to measure the soil half-life of 2,3,7,8-TCDD.

Preliminary findings of studies under way in Finland indicate that 2,3,7,8-TCDD may be slowly biodegraded by anaerobic microorganisms in an organic matrix used for secondary treatment of chlorophenolic wastewaters from paper-pulping operations (Salkinoya-Salonen 1979).

Klecka and Gibson (1979) have recently reported that unsubstituted dibenzo-*p*-dioxin can be readily metabolized by a mutant strain of *Pseudomonas* (sp. N.C.I.B. 9816 strain II) when an alternative source of carbon such as salicylate is available. The dioxin molecule was metabolized first to cis-1,2-dihydroxy-1,2-dihydrodibenzo[1,4]dioxan (I), which was subsequently dehydrated to yield 2-hydroxydibenzo[1,4]dioxan (II) as the major metabolite. The authors reported finding no organisms capable of utilizing dibenzo-*p*-dioxin as a sole carbon source.



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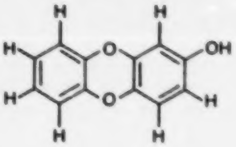

II

PHOTODEGRADATION

Photodegradation is the process of breaking chemical bonds with light. The process, also known as photolysis, involves the breakdown of a chemical by light energy, usually in a specific wavelength range. In photodegradation of dioxins, the ultraviolet wavelengths of light have been shown to be the most effective.

In most photolysis studies, scientists are interested in determining one or more of the following parameters:

1. Photolysis reaction rates
2. Photolysis reaction products
3. Wavelength(s) required for photolysis
4. Other specific conditions required for photolysis

The photolysis of chlorinated aromatic compounds usually involves loss of a chlorine molecule to a free radical, or loss through nucleophilic displacement if a solvent or substrate molecule is present. These mechanisms may be influenced by the presence of other reagents or the nature of the reaction medium.

Photolysis studies have clearly shown that dioxins may be photolytically degraded in the environment by natural sunlight. The extent to which this mechanism actually removes or degrades dioxins in the "real-world" environment is difficult to assess, but of all the possible natural removal mechanisms, photolysis appears to be the most significant. It should be noted that photolysis apparently results in the removal of one or more chlorine atoms from the dioxin molecule. Removal of chlorine from 2,3,7,8-TCDD may make it less toxic, but it has been speculated that the basic dioxin structure remains. When penta-CDD is photodegraded, it may go to a TCDD isomer. (For further discussion see pp. 263–264 of Section 8.)

Several dioxin photodegradation studies are discussed in the paragraphs that follow. Major findings from these studies are summarized in Tables 49 and 50.

Crosby et al. (1971) studied photolysis rates of 2,3,7,8-TCDD, 2,7-DCDD, and OCDD dissolved in methanol. Samples were irradiated with natural sunlight or artificial sunlight with a light intensity of 100 MW/cm^2 at the absorption maximum of 2,3,7,8-TCDD (307 nm). Irradiation of a single solution of 2,3,7,8-TCDD in methanol for 24 hours in natural sunlight resulted in complete photolysis to less-chlorinated dioxin isomers. The degradation of 2,7-DCDD was at least initially more rapid than that of 2,3,7,8-TCDD. After 6 hours of irradiation in artificial ultraviolet light, about 30 percent of the 2,7-DCDD remained unreacted whereas almost 50 percent of the 2,3,7,8-TCDD remained unreacted. The amount of 2,7-DCDD remaining after 24 hours was not reported. The OCDD was photolyzed much more slowly than the TCDD or DCDD isomers; after 24 hours, over 80 percent of the initial OCDD (2.2 mg/liter) remained unreacted. Analysis of reaction products indicated chlorinated dioxins of reduced chlorine content.

In another study the degradation of OCDD on filter paper was reported as being more rapid in natural sunlight than in artificial ultraviolet light (Arsenault 1976). Degradation of OCDD also proceeded more rapidly in the presence of mineral oil or a petroleum oil solvent than in the absence of oil. When OCDD in oil was exposed to natural sunlight, 66 percent was decomposd in as little as 16 hours. When exposed in the absence of oil, only 20 percent was decomposed within 16 hours. No TCDD's were found in the decomposition products.

The same report describes a study of the rate of OCDD degradation on the surfaces of wooden poles treated with PCP-petroleum and Cellon. Preliminary results show that the OCDD is rapidly degraded. Breakdown products are not reported.

In tests involving exposure of a crystalline water suspension of 2,3,7,8-TCDD to a sunlamp, the insolubility of the dioxin caused difficulties. Irradiation apparently had no effect on the water suspension. A crystalline state may prohibit the loss of chlorine or obstraction of hydrogen atoms from each other (Plimmer 1978a).

When a benzene solution of 2,3,7,8-TCDD was added to water stabilized with a surfactant and irradiated with a sunlamp, the dioxin content was reduced (Plimmer et al. 1973).

TABLE 49. PHOTODEGRADATION OF 2,3,7,8-TCDD

Physical conditions	Light source	Length of exposure	Amount degraded (%)	Reaction products	Reference
TCDD in methanol	Artificial (100 μw/cm^2)	24 h	100	Trichlorodibenzo-*p*-dioxin Dichlorobenzo-*p*-dioxin	Crosby et al. 1971
TCDD in methanol	Natural sunlight	7 h	100	NR[a]	Crosby et al. 1971
TCDD (crystalline) in water	Artificial (sunlamp)	NR	0	NA[b]	Crosby et al. 1973
TCDD on soil		96 h	0		
TCDD in benzene/water/surfactant	Artificial (sunlamp)	NR	>0	NR	Plimmer et al. 1973
TCDD crystals on glass plate	Natural sunlight	14 days	0	NR	Crosby et al. 1971
TCDD in isooctane and 1-octanol	Artificial (G.E. RS sunlamp)	40 min	50	NR	Stehl et al. 1973
		24 h	100	NR	Stehl et al. 1973
TCDD in Herbicide Orange, on glass	Natural sunlight	6 h	60		Crosby and Wong 1977
TCDD in commercial Esteron herbicide, on glass	Natural sunlight	6 h	70	NR	Crosby and Wong 1977
TCDD in Esteron base, on glass	Natural sunlight	2 h	90		Crosby and Wong 1977

(continued)

TABLE 49. (continued)

Physical conditions	Light source	Length of exposure	Amount degraded (%)	Reaction products	Reference
TCDD in Herbicide Orange, on plant leaves	Sunlight	6 h 6 h	100 70		Crosby and Wong 1977
TCDD in Herbicide Orange, on soil	Sunlight	6 h	10		Crosby and Wong 1977
TCDD on silica gel	Artificial λ >290 nm	7 days	92	NR[a]	Gebefuigi 1977
TCDD on silica gel	Artificial λ = 230 nm	7 days	98	NR	Gebefuigi 1977
TCDD in Seveso soil with ethyl oleate-xylene mixture	Sunlight artificial (Phillips MLU 300 W)	7 days 3 days	>90 100	NR	Bertoni 1978
TCDD in 1-hexadecylpyridinium chloride (CPC)	Artificial	4 h	>90	NR	Botre et al. 1978
TCDD in sodium dodecylsulfate (SDS)	Artificial	4 h 8 h	≅50 ≅100	NR NR	Botre et al. 1978
TCDD in methanol	Artificial	4 h 8 h	≅50 ≅75	NR NR	Botre et al. 1978

(continued)

TABLE 49. (continued)

Physical conditions	Light source	Length of exposure	Amount degraded (%)	Reaction products	Reference
TCDD in Seveso soil/treated with aqueous olive oil solution or olive oil/cyclohexanone	Natural sunlight	9 days	>90	NR	Crosby 1978
TCDD in emulsifiable silvex formulation	Natural sunlight	≅8 days	50	NR	Nash and Beall 1978
TCDD in granular silvex formulation	Natural sunlight	≅13.5 days	50	NR[a]	Nash and Beall 1978

a—NR = Not reported.
b—NA = Not applicable.

TABLE 50. PHOTODEGRADATION OF DCDD AND OCDD

Physical conditions	Light source	Length of exposure	Amount degraded (%)	Reaction products	Reference
OCDD in methanol	Artificial UV light (100 μw/cm^2)	24 h	>20	Series of chlorinated dioxins of decreasing chlorine content	Crosby et al. 1971
OCDD on filter paper	Artificial sunlight Natural sunlight	NR[a]	More rapid in natural sunlight than artificial UV light	NR	Arsenault 1976
OCDD in oil (mineral or petroleum)	Natural sunlight	16 h	66	NR	Arsenault 1976
OCDD—no oil	Natural	16 h	20	NR	Arsenault 1976
OCDD/benzene-hexane	Mercury UV lamp	4 h	70	Hexa-CDD, hepta-CDD, penta-CDD	Buser 1976
OCDD/benzene-hexane	Mercury UV lamp	24 h	90	Hexa-CDD, hepta-CDD, penta-CDD, TCDD (trace)	Buser 1976
OCDD in isooctane	Artificial UV light	18 h	20	NR	Stehl et al. 1973
OCDD in 1-octanol	Artificial UV light	20 h	6	NR	Stehl et al. 1973
DCDD in methanol	Artificial UV light	≅6 h	≅70	NR	Crosby et al. 1971
DCDD in isooctane and 1-octanol	Artificial UV light	40 min	50	NR	Stehl et al. 1973

a—NR = Not reported.

In another study when 2,3,7,8-TCDD was applied to dry or moist soil, irradiation caused no change after 96 hours. Similar results were obtained by applying this substance to a glass plate and irradiating up to 14 days (Crosby et al. 1971).

Buser (1976) irradiated samples of a solution of OCDD in benzene-hexane for 1 to 24 hours with a mercury ultraviolet lamp. After 4 hours of exposure, 30 percent of the OCDD remained unchanged; the major reaction products were hexa- and hepta-CDD's and trace amounts of penta-CDD's. After 24 hours of irradiation, the hexa- and hepta-CDD's still constituted the major reaction products, with significant amounts of penta-CDD's and trace amounts of TCDD's. Only 10 percent of the initial OCDD remained unchanged. It was concluded that since some commercial products contain up to several hundred ppm of the octa- and hepta-CDD's, photolytic formation of more toxic polychlorinated dioxins could have environmental significance.

Exposure of TCDD's and DCDD's in isooctane and 1-octanol to artificial sunlight (General Electric RS sunlamp) showed that both substances had half-lives of about 40 minutes in each solvent (Stehl et al. 1973). Analysis of the mixtures after 24 hours of irradiation showed no 2,3,7,8-TCDD at a detection limit of 0.5 ppm. A bioassay of rabbit ear skin tissue to which the photolysis products had been applied revealed no chloracnegenic activity.

When a solution of OCDD and isooctane was exposed to artificial sunlight, about 80 percent of the OCDD remained unreacted after 18 hours. With a solution of OCDD and 1-octanol, about 94 percent of the OCDD remained unreacted after 20 hours (Stehl et al. 1973).

In a series of tests, thin layers of Herbicide Orange containing 15 ppm 2,3,7,8-TCDD were exposed to summer sunlight in glass petri dishes (Crosby and Wong 1977). After 6 hours, just over 40 percent of the dioxin remained. A commercial herbicide composed of butyl esters of 2,4-D and 2,4,5-T and containing 10 ppm 2,3,7,8-TCDD was exposed in the same manner; after 6 hours only about 30 percent of the initial dioxin remained. A commercial mixture containing no herbicides, but with 10 ppm 2,3,7,8-TCDD was also exposed to sunlight on glass petri dishes. The original dioxin concentration was reduced by about 90 percent after 2 hours. Herbicide Orange was applied in droplets to excised rubber plant leaves and to the surface of Sacramento loam soil; the samples were then exposed to sunlight. At an application rate of $6.7 mg/cm^2$ of leaf surface, no TCDD's were detected on the leaves after 6 hours. At a lower application rate of $1.3 mg/cm^2$, however, about 30 percent of the TCDD's remained after 6 hours. It was also reported that upon application to the soil ($10 mg/cm^2$) approximately 90 percent of the dioxin remained after 6 hours. The authors attributed the lesser degree of photolysis of 2,3,7,8-TCDD on the soil partly to shading of lower layers by soil particles.

Investigators in this study concluded that there are three requirements for dioxin photolysis:

1. Dissolution in a light-transmitting film
2. Presence of an organic hydrogen donor
3. Ultraviolet light

In another study, 2,3,7,8-TCDD deposited on silica gel was irradiated with light having a wavelength greater than 290 nm. The original concentration of the dioxin was reduced by 92 percent after 7 days. When irradiation was done with light of shorter wavelength (>230 nm), the dioxin concentration was reduced by 98 percent after 7 days. It was concluded that cleavage of 2,3,7,8-TCDD was possible without a proton donor if the intensity of the sun at ground level was great enough to supply the required irradiation (Gebefuigi, Baumann, and Korte 1977).

In a study reported by Bertoni et al. (1978) about 150 ml/m^2 of an ethyloleate-xylene mixture was sprayed on a 1-cm-deep sample of Seveso soil contaminated with 2,3,7,8-TCDD. More than 90 percent of the 2,3,7,8-TCDD was destroyed after 7 days of sunlight exposure. When a dioxin sample was placed in a room sprayed with ethyloleate-xylene mixture, disappearance of the dioxin was almost complete after 3 days exposure under a Phillips MLU 300 W lamp. The xylene was used to reduce viscosity, although ethyloleate was just as effective when used alone. The more rapid photolysis in the room was attributed mainly to the smooth walls of the room receiving the full intensity of the radiation, including the wavelength of light that was absorbed most readily by dioxins.

The smooth gradual decrease of dioxin concentration in the 1-cm-deep soil samples was unexpected because ultraviolet light does not penetrate soil. It was hypothesized that dioxin decomposition below the soil surface could result either from a diffusion mechanism in the oleate medium or from photolytic reactions occurring through long-lived free radicals.

The solubility and photodecomposition of 2,3,7,8,-TCDD in cationic, anionic, and nonionic surfactants was studied by use of both pure dioxin samples and contaminated materials obtained from the Seveso area (Botre, Memoli, and Alhaique 1979). To test the effectiveness of the solubilizing agents, homogeneous soil samples were treated twice with surfactant and then three times with the same volume of water to remove the surfactant. Extracts from the residual soil were then obtained with benzene and methanol, and the extracts were analyzed for 2,3,7,8-TCDD. Untreated contaminated soil samples were used for standards. In the pure dioxin solubilization study, 4 ml of surfactant was used to treat the residues. Methanol was used as the reference solvent. The surfactants used were sodium dodecyl sulfate (SDS), and anionic surfactant, 1-hexadecylpyridinium sorbitan monooleate (Tween 80), hexadecyltrimethylammonium bromide, and 1-hexadecylpyridinium chloride (CPC).

Results showed that CPC was the best solubilizing agent for contaminated soil taken from the Seveso area, whereas in the pure dioxin experiment the differences were slight. Photodecomposition experiments performed using 2,3,7,8-TCDD dissolved in surfactants and in methanol also revealed CPC as the superior medium. Irradiation with an ultraviolet lamp for 4 hours destroyed about 90 percent of the dioxin in the CPC solution. Only 50 percent of the dioxin in the SDS solution was destroyed after 4 hours of irradiation, although almost 100 percent disappeared after 8 hours. Over 25 percent of the dioxin in methanol remained after 8 hours.

In a small-scale study in Seveso, olive oil was used in either a 40 percent aqueous emulsion or an 80 percent cyclohexanone solution and applied on a heavily contaminated area of grassland. These solutions supplied a hydrogen donor in an effort to facilitate photodegradation of the dioxin present. It was reported that after 9 days 80 to 90 percent of the 2,3,7,8-TCDD was destroyed, whereas concentrations in controls remained virtually unchanged (Wipf et al. 1978; Crosby 1978).

In a study of the fate of 2,3,7,8-TCDD in an aquatic environment, samples of lake sediment and water containing ^{14}C-labeled 2,3,7,8-TCDD were incubated in glass vials under light and dark conditions for 39 days (Matsumura and Ward 1976). Results indicated no significant photolytic destruction of the dioxin. Whether artificial or natural light was used is not mentioned.

The fate of 2,3,7,8-TCDD in emulsifiable and granular silvex formulations was studied after application to microagroecosystems and outdoor field plots (Nash and Beall 1978). (Experimental conditions of this study are described more completely in the subsection on physical transport.) It was observed that upon volatilization, the dioxin in both the emulsifiable and granular formulations was photolyzed not only in direct sunlight but also in shaded areas outdoors and in filtered sunlight passing through the glass of the microagroecosystem chambers.

The mean half-life of the dioxin in the emulsifiable concentrate was approximately 7.65 days; the half-life in the granular formulation was 13.5 days. The half-life of the dioxin in the emulsifiable formulation on grass in a microagroecosystem ranged from 5 to 7.5 days.

Crosby and Wong reported in 1973 that the major photodecomposition products of 2,4,5-T are 2,4,5-TCP, 2-hydroxy-4, 5-dichlorophenoxyacetic acid, 4,6-dichlororesorcinol, 4-chlororesorcinol, and 2,5,-dichlorophenol; 2,3,7,8-TCDD was not detected as a photolysis product.

PHYSICAL TRANSPORT

This section describes studies of the movement of dioxins in or into soil, water, and air. Because of episodes involving actual contamination, such movement has become a critical issue. The transport of a chemical in the environment depends greatly upon the properties of the chemical: Is it soluble in water? Is it volatile? Does it cling to soils readily? With the answers to these questions, it is possible to at least postulate reasonably where these chemicals might be found following release into the environment and by what means human or animal receptors are most likely to be affected.

Transport in Soil

Many studies have addressed the mobility of dioxins, especially 2,3,7,8-TCDD, in soils. Generally it has been found that dioxins are more tightly bound to soils having relatively higher organic content. Dioxins applied to the surface of such soils generally remain in the upper 6 to 12 inches. They migrate more deeply into more sandy soils, to depths of 3 feet or more. In areas of heavy rainfall, not only is vertical migration enhanced but lateral displacement also occurs by soil erosion with runoff and/or flooding. Dioxins may appear in normal water leachate from soils that have received several dioxin applications.

Kearney et al. (1973b) studied the mobility of 2,7-DCDD and 2,3,7,8-TCDD in five different types of soil. They observed that the mobility of both dioxins decreased with increasing organic content of the soil. Based on this observation and the finding that these dioxins were relatively immobile in the soils tested, the conclusion was that these dioxins would pose no threat to groundwater supplies because they would not be mobilized deep into soils by rainfall or irrigation.

Similar conclusions were reached by Matsumura and Benezet (1973), who showed that mobility of 2,3,7,8-TCDD is relatively slow, much slower than that of DDT. It was concluded that any movement of 2,3,7,8-TCDD in the soil environment would be by horizontal transfer of soil and dust particles or by biological transfer (other than by plants).

During the 8-year period from 1962 to 1970, the U.S. Air Force sprayed 170,000 pounds of 2,4-D, and 161,000 pounds of 2,4,5-T, in two herbicide formulations (Herbicide Orange and Herbicide Purple) over a test area 1 mile square at the Eglin Air Force Base in Florida (Commoner and Scott 1976). A map of this area is shown in Figure 64. Originally, the applications were done for the purpose of testing spray equipment to be used in Vietnam (Young 1974). The exact concentration of 2,3,7,8-TCDD in the herbicides used for the spraying tests is not known but is estimated to have ranged from 1 to 47 ppm. The test site has since been analyzed for dioxin residues. In 1970 a 36-in.-deep soil core was taken from a portion of the test area that had received approximately 947 pounds per acre of the 2,4-D, 2,4,5-T Herbicide Orange mixture (Woolson and Ensor 1973). At the limits of detection (0.1 to 0.4 ppb), no 2,3,7,8-TCDD was found at any depth. Several explanations were presented for the absence of dioxin: 1) the 2,4,5-T applied contained less than 2 ppm of 2,3,7,8-TCDD, a concentration undetectable in the soil by the analytical method used; 2) the dioxin had migrated to a depth below 36 inches because of the

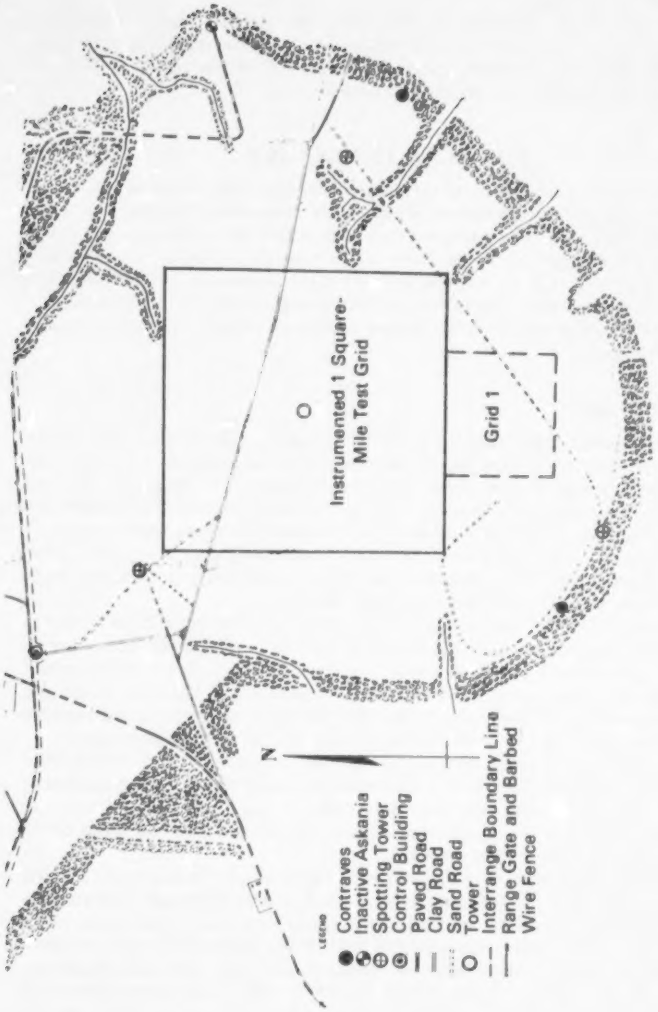

Figure 64. Map of Test Area C-52A, Eglin Air Force Base Reservation, Florida.

Source: Young, Thalken, and Ward 1975.

sandy nature of the soil and the high incidence of rainfall in the area; 3) wind erosion had displaced the dioxin; and 4) biological and/or photochemical decomposition had occured.

In 1973, four soil samples were taken from the same test area and analyzed at low levels for 2,3,7,8-TCDD (Young 1974). The samples contained the dioxin in approximate concentrations of 10, 11, 30, and 710 ppt, and these concentrations were confined to the upper 6 in. of the soil layer.

From March, 1974, to February, 1975, the Air Force performed another study at the Eglin Air Force Base (Bartleson, Harrison, and Morgan 1975). Two test areas were studied, and also an area where the herbicides had been stored and loaded onto planes. The original 1-mile-square area sampled in 1971 and 1973 contained dioxin in concentrations up to 470 ppt. A second test area, designated Grid 1, contained concentrations of 2,3,7,8-TCDD as high as 1500 ppt. The highest dioxin concentrations were generally found in low-lying areas, and the lowest concentrations usually were in areas of loose sand; these findings indicate that the horizontal translocation had probably occurred through water runoff and wind and water erosion.

The storage and loading area contained up to 170,000 ppt of 2,3,7,8-TCDD. This area was elevated relative to a nearby pond. Limited sampling of the pond silt revealed a maximum concentration of 85 ppt, and 11 ppt was found in the pond drainage stream. These findings also indicated horizontal translocation of the dioxin, probably as a result of soil erosion.

A core sample of soil taken from Grid 1 in 1974 showed the following concentrations of 2,3,7,8-TCDD:

Sample depth, in.	Concentration, ppt
0-1	150
1-2	160
2-4	700
4-6	44

These data indicate some vertical movement of 2,3,7,8-TCDD, probably as a result of water percolation through the soil.

In another test, application of 0.448 kg/m² of Herbicide Orange to a test site in Utah resulted in the following concentrations of 2,3,7,8-TCDD 282 days after application:

Sample depth, in.	Concentration, ppt
Control 0-6	<10
0-6	15,000
6-12	3,000
12-18	90
18-24	120

In 1978, additional measurements at the Utah test site were reported (Young et al. 1978). Table 51 presents analytical results of plot sampling 4 years after application of Herbicide Orange at various rates. Table 52 gives results of a similar test performed at Eglin Air Force Base in Florida.

In the tests reported in Tables 51 and 52, samples were taken by means of a soil auger. Subsequent tests revealed that dioxin-containing soil was being carried downward as a result of the auger sampling technique and that the concentrations of 2,3,7,8-TCDD below 6 in. were not detectable.

Followup studies of the residual levels of 2,3,7,8-TCDD in three loading areas of Eglin Air Force Base were conducted during the period from January 1976 to December 1978 (Harrison, Miller, and Crews 1979). Two of the loading areas were relatively free of contamination. The third (described above) had surface

TABLE 51. CONCENTRATIONS OF 2,3,7,8-TCDD AT UTAH TEST RANGE 4 YEARS AFTER HERBICIDE ORANGE APPLICATIONS[a] (parts per trillion)

	Rate of Herbicide Orange application (lb/acre)		
Soil depth (inches)	1000	2000	4000
0-6	650	1600	6600
6-12	11	90	200
12-18	NA[b]	NA	14

a—Source: Young et al. 1978.
b—NA = Not analyzed.

TABLE 52. CONCENTRATIONS OF 2,3,7,8-TCDD AT EGLIN AIR FORCE BASE 414 DAYS AFTER HERBICIDE ORANGE APPLICATION[a]

Soil depth (inches)	Herbicide Orange (ppm)	2,3,7,8-TCDD concentration in soil (ppt)
0-6	1866	250
6-12	263	50
12-18	290	<25[b]
18-24	95	<25[b]
24-30	160	<25[b]
30-36	20	<25[b]

a—Source: Young et al. 1976.
b—Detection limit.

soil concentrations of TCDD's as high as 275 ppb. TCDD's were found at 1 meter depths at concentrations one-third the surface amount.

The accident at Seveso in July 1976 released quantities of 2,3,7,8-TCDD estimated to range from 300 g to 130 kg over an area of approximately 250 acres (Carreri 1978). Because the Seveso soil is drained by an underlying gravel layer, much concern has arisen over the possibility of groundwater contamination. Early soil migration studies in some of the most contaminated areas at Seveso showed that the dioxin penetrated to a depth of 10 to 12 in. Later studies reported by Bolton (1978) found 2,3,7,8-TCDD at soil depths greater than 30 in. An observed 70 percent decrease in 2,3,7,8-TCDD soil concentration over a period of several months may support the suggestion that the dioxin can be mobilized laterally as well as vertically from soils during heavy rainfall or flooding (Commoner 1977).

Following the incident at Verona, Missouri, when oil contaminated with 2,3,7,8-TCDD was sprayed on a horse arena to control dust, the top 12 in. of soil was removed and replaced with fresh soil. After removal and replacement of the soil, no further episodes occurred involving sickness or death of human beings or animals. Investigators concluded that this supported the notion that the vertical mobility of TCDD's is limited (Commoner and Scott 1976).

Nash and Beall (1978) report studies of the fate of 2,3,7,8-TCDD by use of microagroecosystems and outdoor field plots. A diagram of the microagroecosystem is shown in Figure 65. Two commercially available silvex formulations, one granular and one emulsifiable, were tested. The test and control formulations were applied three times to turf in five microagroecosystems and once to turf on the outdoor plots. Throughout the test period a sprinkler system applied water to the soils to simulate rainfall.

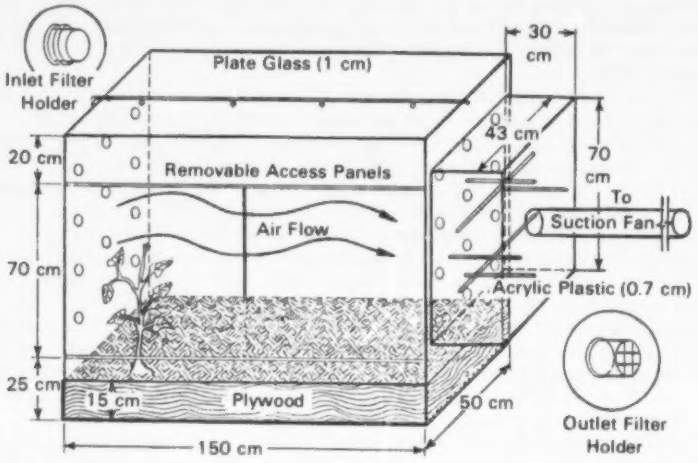

Figure 65. Diagram of microagroecosystem chamber.

The 2,3,7,8-TCDD used in the study was labeled with radioactive hydrogen or ^3H. Throughout the study the labeled dioxin (or breakdown product) was tracked by extremely sensitive radiochemical assay methods. The presence of the dioxin molecule in samples was confirmed by gas-liquid chromatography.

In the first two applications (on days 0 and 35) the concentration of 2,3,7,8-TCDD in the silvex was 44 ppb. In the third application (on day 77) the silvex formulations contained 7500 ppb (7.5 ppm) 2,3,7,8-TCDD. Soil, water, air, grass, and earthworms were analyzed for 2,3,7,8-TCDD at various times following each of the herbicide applications.

Soil analyses showed that most (~80 percent) of the applied 2,3,7,8-TCDD remained in the top 2 cm of the soil. Trace levels at depths of 8 to 15 cm indicated some vertical movement of the dioxin in the soil.

Analysis of water leachate samples from the silvex-treated microagroecosystems following the first two herbicide applications showed no detectable 2,3,7,8-TCDD (limits of detection were 10^{-16} g/g*). The dioxin was detected later, however, following the third herbicide application, and maximum concentrations of 0.05 to 0.06 ppb were calculated to possibly be found in the leachate samples taken 7 weeks after that third application.

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*10^{-16} g/g may also be expressed as 0.1 fg/g (0.1 femtogram per gram). It is equivalent to 0.0001 ppt.

In an ongoing study at Rutgers University, 54 soil-core samples (6 in. in depth) have been taken from samples of turf and sod from areas in the United States having histories of silvex and/or 2,4-D applications. The EPA will analyze the samples for dioxins or herbicide residues. Results are not yet available (Hanna and Goldberg, n.d.).

Transport in Water

Contamination of streams and lakes by 2,3,7,8-TCDD has also been of concern, especially because of the spraying of 2,4,5-T on forests to control underbrush. Possible routes of water contamination from spraying are direct application, drift of the spray, and overland transport after heavy rains. The latter, however, seldom occurs on forest lands because the infiltration capacity of forest floors is usually much greater than precipitation rates (Miller, Norris, and Hawkes 1973).

The transport of dioxin-contaminated soil into lakes or streams by erosion constitutes another possible route of contamination. This is evidenced by the detection of 2,3,7,8-TCDD in water samples from a Florida pond adjacent to a highly contaminated land area (Bartleson, Harrison, and Morgan 1975). Additionally, several laboratory studies have shown that lakes or rivers could become contaminated with minute quantities (ppt) of 2,3,7,8-TCDD and possibly other dioxins through leaching from contaminated sediments. In a study reported by Isensee and Jones (1975), 2,3,7,8-TCDD was adsorbed to soils, which were then placed in aquariums filled with water and various aquatic organisms. Concentrations of the dioxin in the water ranged from 0.05 to 1330 ppt. These values corresponded to initial concentrations of 2,3,7,8-TCDD in the soil ranging from 0.001 to 7.45 ppm. The investigators concluded that dioxin adsorbed to soil as a result of normal application of 2,4,5-T would lead to significant concentrations of 2,3,7,8-TCDD in water only if the dioxin-laden soil was washed into a small pond or other small body of water.

Other investigations have shown similar results. Using radiolabeled 2,3,7,8-TCDD, Matsumura and Ward (1976) showed that, after separation from lake-bottom sediment, water contained 0.3 to 9 percent of the original dioxin concentration added to the sediment. Results of another test indicated that a total of about 0.3 percent of the applied dioxin concentration passed through sand with water eluate (Matsumura and Benezet 1973). In some cases, the observed concentration of TCDD's in the water was greater than its water solubility (0.2 ppb). The 1976 report suggests that some of the radioactivity apparent in the aqueous phase was probably due to a combination of lack of dioxin degradation, presence of 2,3,7,8-TCDD metabolites, and binding or adsorption of TCDD's onto organic matter or sediment particles suspended in the water.

In another study, application of ^{14}C-TCDD to a silt loam soil at concentrations of 0.1 ppm led to ^{14}C-TCDD concentrations in the water ranging from 2.4 to 4.2 ppt over a period of 32 days (Yockim, Isensee, and Jones 1978).

The findings of such investigations are consistent with recent reports that TCDD's are migrating to nearby water bodies from industrial chlorophenol wastes buried or stored in various landfills. At Niagara Falls, New York, for example, 1.5 ppb TCDD's have been detected at an onsite lagoon at the Hyde Park dump where 3300 tons of 2,4,5-TCP wastes are buried (Chemical Week 1979a; Wright State University 1979a,b). Sediment from a creek adjacent to the Hyde Park fill (also in the Niagara Falls area) is also contaminated with ppb levels of the dioxin (Chemical Week 1979a, 1979d). In Jacksonville, Arkansas, there is growing evidence that TCDD's may have migrated from process waste containers in the landfill of a former 2,4,5-T production site. The dioxins have been found both in a large pool of surface water on the site (at 500 ppb) and downstream of the facility in the local sewage treatment plant, in bayou-bottom sediments, and in the flesh of mussels and fish (Richards 1979; Fadiman 1979; Cincinnati Enquirer 1979; Tiernan et al. 1980). TCDD's apparently are also being leached into surface and groundwaters from an 880-acre dump site of the Hooker Chemical Company at Montague, Michigan (Chemical Week 1979c; Chemical Regulation Reporter 1979b). Dioxins were found at the site at levels approaching 800 ppt.

Transport in Air

One study has been identified in which levels of 2,3,7,8-TCDD in air have been measured (Nash and Beall 1978). Femtogram (10^{-15} g) quantities of the dioxin were detected in the air after granular and emulsifiable silvex formulations containing radiolabeled 2,3,7,8-TCDD had been applied to microagroecosystems. Air concentrations of the dioxin decreased appreciably with time following application. The data appear to confirm that TCDD has a very low vapor pressure and that loss due to volatilization is extremely low, especially when low levels of 2,3,7,8-TCDD are involved and granular formulations containing the dioxin are used.

Results of other investigations indicate that water-mediated evaporation of TCDD's may take place (Matsumura and Ward 1976).

Transport of dioxins by way of airborne particulates has recently received much attention. Several studies have shown the presence of dioxins in fly ash from municipal incinerators (Nilsson et al. 1974; Olie, Vermuelen, and Hutzinger 1977; Buser and Rappe 1978; Dow Chemical Company 1978; Tiernan and Taylor 1980). A recent report of Dow Chemical Company (1978) contends that particulates from various combustion sources may contain dioxins and that these dioxin-laden particulates are a significant source of dioxins in the environment. More details on these studies are presented in Section 3.

It has also been recently reported that dioxins from buried chlorophenol wastes are being mobilized by means of airborne dust particles (Chemical Regulation Reporter 1980a).

BIOLOGICAL TRANSPORT

This section discusses the potential for dioxins to accumulate and to become concentrated and magnified in biological tissues. In the past, pesticides (most notably DDT) have been found to accumulate in organisms at almost every trophic level. In some organisms, these chemicals have been concentrated in the tissues. When an animal in a higher trophic level feeds on organisms that accumulate these chemicals, the animal receives several "doses" of the chemical, resulting in what is termed biomagnification. If this process proceeds to higher levels in the food chain, the chemicals may become concentrated hundreds or thousands of times, with possibly disastrous consequences.

The ability for a chemical to accumulate and to become concentrated or participate in biomagnification depends primarily on its availability to organisms, its affinity for bioligical tissues, and its resistance to breakdown and degradation in the organism.

Bioaccumulation, Bioconcentration, and Biomagnification in Animals

The biological activity of dioxins with respect to accumulation, concentration, and magnification has been addressed by several researchers. Briefly, bioaccumulation is the uptake and retention of a pollutant by an organism. The pollutant is said to be bioconcentrated when it has accumulated in biological segments of the environment. The increase of pollutant concentrations in the tissues of organisms at successively higher trophic levels is biomagnification.

Several investigators (Fanelli et al. 1979, 1980; Frigerio 1978) have studied the levels of TCDD's in animals captured in the dioxin-contaminated area near Seveso, Italy. Data shown in Table 53 indicate that TCDD's accumulate in environmentally exposed wildlife. All field mice were found to contain TCDD's at whole-body concentrations ranging from 0.07 to 49 ppb (mean value 4.5 ppb). The mice were collected from an area where the soil contamination (upper 7 cm) varied from 0.01 to 12 ppb (mean value 3.5 ppb). These data are in agreement with Air Force studies by Young et al. (described below), which indicate that rodents living on dioxin-contaminated land concentrate TCDD's in their bodies only to the same order of magnitude as the soil itself; biomagnification does not occur. Several rabbits and one snake have been found to concentrate TCDD's in the liver. The snake also had accumulated a very high level of TCDD's in the adipose (fat) tissue. Liver samples from domestic birds were analyzed for TCDD's with negative results.

TABLE 53. TCDD LEVELS IN WILDLIFE[a]

Animal	No. of samples analyzed	Tissue	Positive	TCDD level (ng/g) (ppb) Average	TCDD level (ng/g) (ppb) Range
Field mouse	14	Whole body	14/14	4.5	0.07–49
Hare	5	Liver	3/5	7.7	2.70–13
Toad	1	Whole body	1/1	0.2	
Snake	1	Liver	1/1	2.7	
		Adipose tissue	–	16.0	
Earthworm	2[b]	Whole body	1/2	12.0	

a—Source: Fanelli et al. 1980.
b—Each sample represents a 5-g pool of earthworms.

Earlier studies by the Air Force evaluated alternative methods for disposal of an excess of 2.3 million gallons of Herbicide Orange left from the defoliation program in Southeast Asia. The studies took place at the test site at Eglin Air Force Base in Florida (Figure 64) and at test areas in Utah and Kansas.

In June and October of 1973, samples of liver and fat tissue of rats and mice collected from grids on a 3-mile-square test area (TA C-52A) at Eglin Air Force Base were analyzed for the presence of TCDD's (Young 1974). The samples contained concentrations of TCDD's ranging from 210 to 542 ppt. Tissue of control animals contained less than 20 ppt TCDD's. Because most of the concentrations of TCDD's in the group of animals tested were higher than those found in the soil, it was suggested that biomagnification might have occurred; however, because the animals studied failed to show teratogenic or pathologic abnormalities, the presence of a substance similar to TCDD's but with a lower biologic activity was postulated.

Another Air Force report gives results of additional studies conducted at Eglin Air Force TA C-52A (Young, Thalken, and Ward 1975). In an effort to test the possible correlation between levels of TCDD's in the livers of beach mice and in soil, experiments were conducted to determine the possible exposure routes. Because contamination by TCDD's could be detected only in the top 6 in. of soil, it was thought that a food source might be responsible for the presence of the dioxin in animal tissue. Analysis of seeds (a food source for beach mice) collected in the area revealed no TCDD's (at 1 ppt detection level); therefore, another route of contamination was suggested. Since the beach mouse spends as much as 50 percent of its time grooming, investigators postulated that the soil adhering to the fur of the mice as they move to and from their burrows was being ingested. As a test of this hypothesis, a dozen beach mice were dusted 10 times over a 28-day period with alumina gel containing TCDD's. Analysis of pooled samples of liver tissue from controls indicated concentrations of TCDD's of less than 8 ppt (detection limit), whereas concentrations in samples of tissue from the dusted mice reached 125 ppt.

Further analysis was done on samples of liver tissue from beach mice collected from Grid 1 of TA C-52A. A composite sample of male and female liver tissue contained TCDD's at levels of 520 ppt, and a composite sample of male tissue contained 1300 ppt. In contrast, the liver tissue of mice collected from control field sites contained TCDD's in concentrations ranging from 20 ppt (male and female composite) to 83 ppt (female composite). Air Force researchers concluded that although bioaccumulation was evident, there were no data to support biomagnification because the levels of TCDD's in the liver tissue of beach mice were in general no greater than levels found in the soil on Grid 1 (ranging from <10 to 1500 ppt).

In evaluation of this Air Force study Commoner and Scott (1976) again reached a different conclusion. Because dioxin concentrations in the pooled liver samples represented an average value for the mice, they believed that this value should be compared with average value for TCDD's in the soil of Grid 1, which was 339 ppt. They concluded that biomagnification was evidenced by the significantly higher levels of TCDD's in mouse liver than in soil.

Analysis for TCDD's in the six-lined racerunner, a lizard found in the area, showed concentrations of 360 ppt in a pooled sample of viscera tissue and 370 ppt in a pooled sample of tissue from the trunks of specimens captured in TA C-52A. Specimens captured at a control site showed concentrations of TCDD's less than 50 ppt (detection limit).

Early studies of aquatic specimens obtained from ponds and streams associated with TA C-52A showed no TCDD's at a detection limit of less than 10 ppt (Young 1974). In further studies, however, three fish species showed detectable (ppt) levels of TCDD's (Young, Thalken, and Ward 1975). Pooled samples of skin, gonads, muscle, and gut from a species of bluegill, *Lepomis puntatus*, contained 4, 18, 4, and 85 ppt TCDD's, respectively. All of these specimens were obtained from the Grid 1 pond on TA C-52A, where bluegill was at the top of the food chain. Two other fish species, *Notropis lypselopterus* (sailfin shiner) and *Gambusia affinis* (mosquito fish), also showed 12 ppt of TCDD's. These specimens were collected from Trout Creek, a stream draining Grid 1. (Mosquito fish samples consisted of bodies minus heads, tails, and viscera, whereas shiner samples consisted of gut.) Inspection of gut contents of *Lepomis* specimens from Trout Creek showed that the food source of this fish consisted mostly of terrestrial insects. The source of the TCDD's was not identified, however.

In another Air Force study, tests were done on 22 biological samples from TA C52A and 6 samples (all fish) from the pond at the hardstand-7 loading area designated as HS-7 (Bartleson, Harrison, and Morgan 1975). A composite of whole bodies of 20 mosquito fish *Gambusia* collected from the HS-7 pond and 600 feet downstream showed a concentration of 150 ppt TCDD's. Liver samples from six small sunfish from the HS-7 pond also showed 150 ppt TCDD's, whereas samples of the livers and fat of 12 medium-sized sunfish from the HS-7 pond showed concentrations of 0.74 ppb. Because the solubility of 2,3,7,8-TCDD in water is far below these levels (0.2 ppb), the data seem to indicate biomagnification in addition to bioaccumulation. The stream that drains the HS-7 pond flows north into a larger pond known as Beaver Pond. Composite samples of four whole large fish from Beaver Pond showed a concentration of 14 ppt TCDD's. The livers of 25 large fish and fillets of 8 large fish from Beaver Pond showed no TCDD's at a detection limit of 5 ppt. A followup study conducted from 1976 to 1978 showed that TCDD's were present in turtle fat and beach mouse liver and skin (Harrison, Miller, and Crews 1979).

In the same study, samples obtained from deer, meadowlark, dove, opposum, rabbit, grasshopper, six-lined racerunner, sparrow, and miscellaneous insects from TA C-52A were analyzed for TCDD's. TCDD's were detected in the livers and stomach contents of all of the birds. One composite sample of meadowlark livers contained 1020 ppt TCDD's, the highest level found in all samples. No TCDD's were detected in samples from deer, oppossum, or grasshopper. The sample from miscellaneous insects contained 40 ppt TCDD's, and the composite sample from racerunners, 430 ppt TCDD. The authors concluded that this study demonstrated bioaccumulation. The data also indicate that biomagnification may have occurred. Commoner and Scott (1976b) point out that the average concentration of TCDD's in soil from TA C-52A was 46 ppt.It should also be noted that the composite insect sample most likely included insects that are eaten by the birds. In all cases the concentration of TCDD's in animal liver samples was greater than that in the insect sample, an indication of the possibility of biomagnification. Because none of the Air Force studies analyzed for TCDD's in a series of trophic levels, biomagnification was not clearly demonstrated.

Woolson and Ensor (1972) analyzed tissues from 19 bald eagles collected in various regions of the country in an effort to determine whether dioxins were present at the top of a food chain. At a detection limit of 50 ppb, no dioxins were found.

Another study failed to show dioxin contamination in tissues of Maine fish and birds (Zitco, Hutzinger, and Choi 1972).

In a similar study 45 herring gull eggs and pooled samples of sea lion blubber and liver were analyzed for dioxins and various other substances (Bowes et al. 1973). Analysis by gas chromatography with electron capture and high-resolution mass spectrophotometry revealed no dioxins.

Fish and crustaceans collected in 1970 from South Vietnam were analyzed for TCDD's in an effort to determine whether the spraying of Herbicide Orange had led to accumulation of TCDD's in the environment (Baughman and Meselson 1973). Samples of carp, catfish, river prawn, croaker, and prawn were collected from interior rivers and along the seacoast of South Vietnam and were immediately frozen in solid CO_2. Butterfish collected at Cape Cod, Massachusetts, were analyzed as controls. Samples of fish from the Dong Nai River (catfish and carp) showed the highest levels of TCDD's, ranging from 320 to 1020 ppt. Samples of catfish and river prawn from the Saigon River showed levels ranging from 34 to 89 ppt. Samples of croaker and prawn collected along the seacoast showed levels of 14 and 110 ppm of TCDD's, whereas in samples of butterfish from Cape Cod the mean concentration of TCDD's was under 3 ppt (detection limit). The authors concluded that TCDD's had possibly accumulated to significant environmental levels in some food chains in South Vietnam.

Other investigators have studied the accumulation of TCDD's in mountain beavers after normal application of a butyl ester of 2,4-D and 2,4,5-T to brushfields in western Oregon (Newton and Snyder 1978). They reported that the home range of the mountain beavers was small and that among all animals collected inside the treatment areas the home ranges centered at least 300 feet from the edge of the treatment area. Thus their food supplies, consisting primarily of sword fern, vine maple, and salmonberry, had definitely been exposed to the herbicide. Analysis of 11 livers from the beavers showed no TCDD's in 10 of the samples at detection limits of 3 to 17 ppt. One sample was questionable; the concentration was calculated at 3 ppt TCDD's.

Investigators in another study analyzed milk from cows that grazed on pasture and drank from ponds that had received applications of 2,4,5-T (Getzendaner, Mahle, and Higgins 1977). Sample collection ranged from 5 days to 48 months after application; 14 samples were collected within 1 year after application. Application rates ranged from 1 to 3 pounds per acre. Milk purchased from a supermarket was used as the control. The control samples contained levels of TCDD's ranging from nondetectable to 1 ppt. No milk samples from cows grazing on treated pasture contained levels of TCDD's above 1 ppt.

In a similar study, milk samples were collected throughout the Seveso area just after the ICMESA accident occurred (Fanelli et al. 1980). The samples were analyzed for TCDD's by GC-MS methods. Results are given in Table 54. Figure 66 shows the sites where the milk samples were collected. Dioxin levels were highest in samples from farms close to the ICMESA plant. The high levels of TCDD's found in the milk samples strongly suggest that human exposure via oral intake must have occurred after the accident through consumption of dairy products. A milk monitoring program that has been sampling milk from outside Zone R since 1978 no longer detects TCDD's in any of the samples.

Three research teams have analyzed fat from cattle that had grazed on land where 2,4,5-T herbicides were applied. In one study, five of eight samples collected from the Texas A & M University Range Science Department in Mertzon, Texas, showed the possible presence of TCDD's at low ppt levels when analyzed by gas chromatography/low-resolution mass spectrometry (Kocher et al. 1978).

TABLE 54. TCDD LEVELS IN MILK SAMPLES COLLECTED NEAR SEVESO IN JULY-AUGUST 1976[a]

Map number[b]	Date of collection	TCDD concentration (ng/liter) (ppt)
1	7/28	76
2	7/28	7919
	8/2	5128
	8/10	2483
3	7/28	469
	8/2	1593
	8/10	496
4	8/10	1000
5	7/29	116
6	7/29	59
7	8/3	80
8	8/3	94
9	7/27	180
	8/3	75
10	8/5	<40

a—Source: Fanelli et al. 1980.
b—Locations shown in Figure 66.

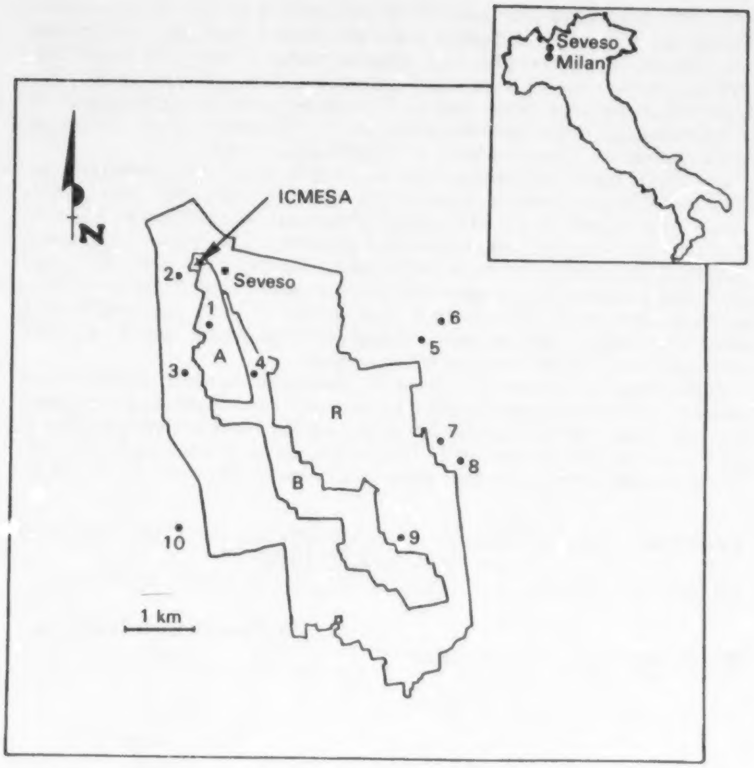

Figure 66. Location of farms near Seveso at which cow's milk samples were collected for TCDD analysis in 1976 (July–August).

Source: Fanelli et al. 1980.

Apparent TCDD concentrations ranged from 4 to 15 ppt at detection limits ranging from 3 to 6 ppt. In the second study, 11 of 14 samples analyzed contained TCDD's (Meselson, O'Keefe, and Baughman 1978). The four highest levels reported were 12, 20, 24, and 70 ppt TCDD. In the third study, Solch et al. (1978, 1980) detected TCDD's in 13 of 102 samples of beef fat at levels ranging from 10 to 54 ppt.

Shadoff and co-workers could find no evidence that TCDD's are bioconcentrated in the fat of cattle (Shadoff et al. 1977). The animals were fed ronnel insecticide contaminated with trace amounts of TCDD's for 147 days. Sample cleanup was extensive to permit low-level detection of the dioxin. Analysis was by combined gas chromatography/mass spectrometry (both high and low resolution). No TCDD's were detected at a lower detection limit of 5 to 10 ppt.

Samples of human milk obtained from women living in areas where 2,4,5-T is used have also been analyzed for dioxins. In one study, four of eight samples were reported to contain about 1 ppt TCDD's (Meselson, O'Keefe, and Baughman 1978). In a subsequent study, no evidence of 2,3,7,8-TCDD contamination was found in 103 samples of human milk collected in western states (Chemical

Regulation Reporter 1980). The lower level of detection in the latter study ranged from 1 to 4 ppt.

Model ecosystems have been developed in aquariums to study the bioaccumulation and concentration of several pesticides including TCDD's (Matsumura and Benezet 1973). Concentration factors for TCDD's calculated from these studies were:

Daphnia: 2198
Mosquito larvae: 2846
Ostracoda: 107
Northernbrook silverside fish: 54

The authors concluded that the biological and physical characteristics of organisms played an important role in the bioaccumulation and concentration of TCDD's and the other pesticides studied. They also indicated that because of the low solubility of TCDD's in water and liquids and their low partition coefficient in liquids, TCDD's are not likely to accumulate in biological systems as readily as DDT.

Another aquatic study involved a recirculating static model ecosystem in which fish were separated from all the other organisms (algae, snails, daphnia) by a screened partition (Yockim, Isensee, and Jones 1978). In this study ^{14}C-TCDD was added to 400 g of Metapeake silt loam clay to yield TCDD's at a concentration of 0.1 ppm. Treated soils were placed in the large chambers of the ecosystem tanks and flooded with 16 l of water. One day after the water addition, all organisms except the catfish were added. Samples of organisms and water were collected on days 1, 3, 7, 15, and 32. On day 15 a second group of 15 mosquito fish was added. On day 32 all organisms remaining were collected and counted. Also on day 32, nine channel catfish were added to the large chambers of the tanks containing the soil. Catfish were collected 1, 3, 7, and 15 days later. Of the two collected on each day, one was sacrificed for analysis and one was placed in untreated water.

Bioaccumulation ratios (tissue concentration of TCDD's divided by water concentration) for the algae ranged from 6 to 2083, the maximum exhibited after 7 days. Bioaccumulation ratios for the snails ranged from 735 to 3731, with the maximum at 15 days. The ratios in daphnia ranged from 1762 to 7125, with the maximum at 7 days. The accumulation ratios in the mosquito fish ranged from 676 at day 1 to 4875 after 7 days. All mosquito fish were dead after 15 days, and their tissues showed an average of 72 ppb TCDD's. No bioaccumulation ratios were calculated for the catfish, but levels of TCDD's in the tissues ranged from 0.9 ppt after day 1 to 5.9 ppt after day 15. By day 32 of exposure, all catfish had died. The average concentration of TCDD's in the tissue at this time was 4.4 ppb.

It was concluded that under normal use of 2,4,5-T, concentration of TCDD's in sediments of natural water bodies would probably be 10^4 to 10^6 times lower than the concentration used in this experiment, and although the TCDD's could be a potential environmental hazard, the magnitude of the hazard would depend on biological availability and persistence in the aquatic ecosystem under conditions of normal use.

In previously mentioned studies with microagroecosystems, earthworms contained 0.2 and 0.3 ppt 2,3,7,8-TCDD and/or breakdown products of TCDD's following two silvex applications to soil (Nash and Beall 1978). The silvex contained 44 ppb TCDD's.

Another study not yet completed concerns the possible accumulation of dioxins in vegetation and earthworms in turf and sod of areas having a history of silvex and/or 2,4-D applications (Hanna and Goldberg, n.d.).

Isensee and Jones (1975) performed three experiments using algae, duckweed, snails, mosquito fish, daphnia, channel catfish and other organisms. Radiolabeled dioxin (^{14}C-TCDD) was adsorbed to two types of soil, which were then placed in glass aquariums and covered with water. One day later, daphnia, algae, snails, and various diatoms, protozoa, and rotifers were added. In one experiment duckweed plants were also added on the second day. After 30 days, some daphnia were analyzed and two mosquito fish were added to each tank. Three days later, all organisms were harvested; in Experiments II and III, two fingerling channel catfish were added to each tank and exposed for 6 days. At the conclusion of each experiment the concentrations of ^{14}C-TCDD in the water and in the organisms were determined and the concentration factors calculated. Table 55 summarizes soil application rates in each experiment and type of soil used.

TABLE 55. SOIL APPLICATION RATES AND REPLICATIONS[a]

Total ^{14}C-TCDD added per tank (μg)	Type of soil[b] and amount of ^{14}C-TCDD added (g)	Final concentrations of ^{14}C-TCDD (ppm)[c]	No. of replicates
	Experiment I		
149	L-20	7.45	3
0	L-20	0.00	1
	Experiment II		
63	L-20	3.17	2
63	L-20 + M-100	0.53	2
63	L-20 + M-200	0.20	2
63	L-20 + M-400	0.15	2
0	L-20	0.00	2
	Experiment III		
10	M-100	0.10	2
1	M-100	0.01	2
0.1	M-100	0.001	2
0.01	M-100	0.0001	2
0	M-100	0.00	2

a—Isensee and Jones 1975.

b—L = Lakeland sandy loam; M = Metapeake silt loam. In Experiment II, L was first treated with ^{14}C-TCDD, then dry-mixed with M in treatment tanks.

c—Soil concentrations based on total quantity of soil in tanks.

At soil concentrations as low as 0.1 ppb, ^{14}C-TCDD was leached into the water and accumulated in the organisms. Bioaccumulation factors at this soil concentration and a water concentration of 0.05 ppt were 2,000 for algae, 4,000 for duckweed, 24,000 for snails, 48,000 for daphnia, 24,000 for mosquito fish, and 2,000 for catfish, corresponding to concentrations of 0.1, 0.2, 1.2, 2.4, and 0.1 ppb of ^{14}C-TCDD in the tissues. Although some biomagnification was evident, results were highly variable. The differences in bioaccumulation factors found in this study relative to those of Yockim et al. (1978) were attributed to system design, differences in the organisms, and the fact that bioaccumulation factors in the other study were based on fresh weight whereas those in this study were based on dry weight.

The authors conclude that since some bioaccumulation ratios were relatively high (as compared with those observed with other pesticides), especially in daphnia and mosquito fish, the potential of TCDD's to accumulate in the environment is considerable. They further project, however, that at suggested application rates of 2,4,5-T, concentrations of TCDD's in the soil would probably not result in accumulation in biological systems unless erosion or runoff from recently sprayed areas is discharged to a small body of water (e.g., a pond).

Dow Chemical Company reported in 1978 on a series of studies to determine whether dioxins are present in the Tittabawassee River, into which Dow discharges treated wastes. In one study, rainbow trout were placed in cages at various locations above and below the Dow Midland plant, in a tertiary effluent stream, and in clear well water. Five of six fish placed in the tertiary effluent stream showed levels of TCDD's ranging from 0.2 to 0.05 ppb. Analysis of whole fish exposed for 30 days at a point 6 miles downstream of the effluent discharge showed concentrations of 0.01 and 0.02 ppb TCDD's. Analysis of whole fish from the tertiary effluent showed levels ranging from 0.05 to 0.07 ppb.

In a laboratory experiment with ^{14}C-2,3,7,8-TCDD, Dow (1978) determined that the bioconcentration factor in rainbow trout was about 6600. Dow also analyzed native catfish taken randomly from various locations in the Tittabawassee River and tributaries. The analyses showed levels of TCDD's ranging from 0.07 to 0.23 ppb, levels of OCDD from 0.04 to 0.15 ppb, and one sample with 0.09 ppb of hexa-CDD. Highest levels of TCDD's and OCDD were found in fish collected from the Tittabawassee at points approximately 1 to 2 miles downstream from Dow. Dow noted that caustic digestion used in sample preparation may have degraded octa-, and hexachlorodioxins. No other fish analyzed contained detectable levels of TCDD's (Dow Chemical Company 1978).

Subsequent to the Dow studies, the U.S. EPA colleted and analyzed fish samples from the Tittabawassee, Grand, and Saginaw Rivers in Michigan (Harless 1980). TCDD's were found in 26 of 35 samples (74 percent) at levels ranging from 4 to 690 ppt. Catfish and carp contained the highest concentrations, while perch and bass had the lowest. Additional information concerning dioxin in fish from different sources can be found on pages 175 and 178.

Accumulation in Plants

Because dioxins are sometimes used in herbicides applied on and near areas where food plants may be growing, it is important to determine whether the dioxins may be incorporated into the plants. Thus far, few studies have been done to determine whether dioxins might accumulate in plants. In the few studies that have considered this question, results seem to indicate that very small amounts are accumulated in plants.

Kearney et al. (1973a) studied the uptake of DCDD's and TCDD's from soil by soybeans and oats. Soil applications of ^{14}C-DCDD (0.10 ppm) and ^{14}C-TCDD (0.06 ppm) were made, and a maximum of 0.15 percent of the dioxins was detected in the above-ground portion of the oats and soybeans. No dioxins were found in the grains harvested at maturity. Application of a solution of Tween 80 (a surfactant) and TCDD's or DCDD's to the leaves of young oat and soybean plants showed no translocation to other plant parts after 21 days.

Studies of the absorption and transportation of TCDD's by plants in the contaminated area near Seveso have been reported (Cocucci et al. 1979). Samples of fruits, new leaves, and, in some cases, twigs and cork were taken from various types of fruit trees a year after the dioxin contamination occurred. TCDD's were found in all samples at $\mu g/kg$ levels. Concentrations in the leaves were 3 to 5 times higher than in the fruits, which had the lowest concentrtions. Levels in the cork samples were generally higher than in the leaves, but not as high as in the twigs. The findings show that the dioxin is translocated from the soil by plants in newly formed organs and suggest that the lower concentrations in fruits and leaves may be due to some form of elimination such as transpiration or ultraviolet photodegradation. The latter possibility would agree with the photolysis results reported by Crosby and Wong in 1977.

Cocucci and co-workers also examined specimens of garden plants such as the carrot, potato, onion, and narcissus. Again $\mu g/kg$ levels of TCDD's were found. In all plants, the new aerial portions appeared to contain less dioxin than the underground portions. Concentrations of TCDD's differed in the inner and outer portions of potato tubers and carrot taproots; the variation was attributed to the prevalence of conductive tissues in these plant parts. The authors again suggested that the relatively low concentrations in the aerial parts of these garden plants were due to an elimination process such as transpiration or photodegradation, or possibly to metabolism of the dioxin by the plants. The elimination hypothesis was supported by the further observation that when contaminated plants were transplanted in unpolluted soil, the dioxin content disappeared.

Young et al. (1976) used specially designed growth boxes to study the uptake of ^{14}C-TCDD by *Sorghum vulgave* plants. After placing Herbicide Orange containing 14 ppm ^{14}C-TCDD under the soil in the growth boxes, 100 plants were grown for 64 days. After 64 days the plants were harvested, extracted with hexane, and analyzed for ^{14}C-TCDD. Some plant samples were also analyzed for ^{14}C-TCDD before hexane extraction by combustion and collection of the CO_2. Anaylsis before extraction showed a concentration of about 430 ppt ^{14}C-TCDD in the plant tissue. After hexane extraction, the concentration of ^{14}C-TCDD in the plant tissue was reported as being not significantly reduced. Young et al. concluded that the relatively high ^{14}C activity in the plant tissue could have been due to the presence of 1) nonhexane-soluble TCDD, 2) a soil biodegradation product of TCDD's that was taken up, 3) a metabolic breakdown product of TCDD's found after plant uptake of the TCDD's, or 4) a contaminant in the original ^{14}C-TCDD stock solution that was taken up by the plant.

As mentioned elsewhere, concentration of ^{14}C-TCDD in algae and duckweed has been observed. Bioaccumulation factors were 2000 and 4000, respectively (Isensee and Jones 1975).

SECTION 8

DISPOSAL AND DECONTAMINATION

GENERAL CONSIDERATIONS

One of the principal unsolved problems that has followed the discovery of dioxins is development of methods for destroying them once they are produced. Many investigators have studied various methods for disposing of commercial chemicals and production wastes that contain these compounds, and further research is needed. Even more important is the need for methods of destroying dioxins after they are released into the environment.

Simple out-of-sight storage has been used on several occasions to dispose of dioxin-contaminated soils and equipment following industrial accidents from the manufacture of 2,4,5-TCP. Soil contaminated by the application of dioxin-containing wastes at Verona, Missouri, was used as fill under a new concrete highway and was also placed in a sanitary landfill. Some was also used as fill at two residential sites, but was later removed and placed elsewhere (Commoner 1976a). The soil contaminated by the accident at Seveso, Italy, was partially removed from moderately contaminated areas and added to the more heavily contaminated areas, which will remain uninhabitable for an indefinite period of time (Reggiana 1977). Following an explosion at Coalite and Chemical Products, Ltd., in England, portions of the plant equipment were buried in an abandoned coal mine (May 1973). Portions of the Phillips Duphar plant in the Netherlands, following its explosion, were encased in concrete and dumped into the ocean (Hay 1976a).

The quantities of TCDD-containing wastes from the normal manufacture of 2,4,5-TCP that have been buried at various sites in the United States are not well documented, although some published figures are available. One company at Verona, Missouri, reportedly disposed of 16,000 gallons of 2,4,5-TCP distillation residues over an 8-month period (Shea and Lindler 1975). A New York company reportedly disposed of 3700 tons of 2,4,5-TCP production wastes at three dumps in the Niagara Falls area over a 45-year period (Chemical Week 1979a). It is estimated that the 3700 tons of waste produced by this company could contain 100 pounds of TCDD (Chemical Week 1979a). An Arkansas facility has been producing 2,4,5-TCP and related products since 1957 and possibly earlier (Sidwell 1976a). Reports indicate that 3000 barrels of TCP wastes are buried or stored on the manufacturing site (Fadiman 1979; Cincinnati Enquirer 1979). Many of these barrels were leaking and contaminating nearby water bodies (Richards 1979a; Tiernan et al. 1980). There are, at this writing, 3000 barrels now stored in an EPA-approved shelter, and none are presently leaking. The correction of the drum problem was completed by Vertac at a cost of about $500,000 (Howard 1980).

Continuation of land disposal is still being proposed as at least a temporary measure, however. Other proposals include chemical fixation, deep well disposal, burial in salt mines, and inclusion of these chemicals with nuclear fission by-products in secured cavities.

Although these practices postpone the need for solving the problems of disposal and decontamination, they offer no permanent solutions. Techniques that may be used to decompose dioxins and thereby remove them permanently from the environment are discussed in this section. The most extensively tested method is incineration, which entails a high-temperature oxidation of the dioxin molecules. Physical methods have also been proposed for some applications; these include the use of solvents or adsorbents to concentrate dioxins into smaller volumes for final disposal by incineration or other methods, and also physical methods of detoxification including exposure to ultraviolet light or gamma radiation. Proposed chemical techniques include the use of ozone or special chloroiodide compounds. Biological degradation techniques are also being considered.

INCINERATION DISPOSAL METHODS

Conventional Incineration

Conventional incineration has reached a high level of development for disposal of pesticides and other highly toxic, hazardous materials (Wilkinson, Kelso, and Hopkins 1978; Ferguson et al. 1975; Ottinger 1973; Scurlock et al. 1975; U.S. EPA 1977a; U.S. EPA 1975a; Duvall and Rubey 1976). It is often preferred over other disposal alternatives (Lawless, Ferguson, and Meiners 1975; Kennedy, Stojanovic, and Shuman 1969), and has been used extensively (Ackerman et al. 1978). Incineration as defined here does not include open, uncontrolled burning, but denotes the use of special furnaces equipped with means for accurate regulation of furnace temperature, supplemental fuel usage, and excess air ratios. Industrial incinerators are also equipped with some form of emission control, often a water scrubber. Incinerator off-gas usually contains only low concentrations of carbon particulates, but does contain chlorine and hydrogen chloride if chlorinated organic chemicals are being burned.

Incinerator operating conditions currently considered adequate for complete destruction of 2,3,7,8-TCDD and most other chlorinated organics are a temperature of at least 1000° C (1932° F) with a dwell time of at least 2 seconds (Tenzer et al.; Wilkinson et al. 1978). Laboratory tests have demonstrated that with a dwell time of 21 seconds, only half of the 2,3,7,8-TCDD in a sample decomposes at 700° C, whereas 99.5 percent decomposes at 800° C (Ton That et al. 1973). This information was apparently generated originally by Dow Chemical Company and quoted by Dr. Ton That and other authors (Crummett 1980). These data were obtained with a quartz tube apparatus. Using differential thermal analysis, two other experimenters have observed that complete destruction occurs between 800° and 1000° C (Kearney et al. 1973b), which agrees with the work of Langer et al. (1973). All of these studies have been conducted with relatively pure samples of dioxins. For incineration of impure mixtures, temperatures above 800° C are especially important because at lower temperatures (300° to 500°C) more TCDD may be formed from precursor material (Rappe 1978).

Incineration is now used to dispose of wastes from pesticide manufacture at the Midland, Michigan, facility of Dow Chemical Company. Stationary and rotary kiln incinerators used at this location can handle almost any solid, semisolid, or liquid waste. Dow has emphasized in a 1978 report to the EPA that complete destruction of dioxins is difficult, in that reducing the concentration of a substance from 1 ppm to the equivalent of 1 ppb necessitates an overall efficiency of 99.9 percent, which in not possible with conventional high-capacity incinerators.

The most extensive incineration of a waste chemical containing dioxins was the destruction of 10,400 metric tons (more than 2 million gallons) of Herbicide Orange left over from military defoliation operations in Southeast Asia (Ackerman et al. 1978). This substance was decomposed in two large incinerators mounted on the *Vulcanus*, a chemical tanker ship operated by a company from the Netherlands. Burning took place in the mid-Pacific ocean. In three separate trips, the herbicide was emptied from steel storage drums to railroad tank cars to the cargo holds of the tanker (the drums were rinsed with diesel fuel, which was added to the herbicide). The ship was then moved to the burn location, and the mixture was incinerated at an average flame temperature of 1500° C with an incinerator residence time of 1 second. Flow of combustion air was regulated to maintain a minimum of 3 percent oxygen in the stack gases. Combustion efficiency was about 99.9 percent. Stack effluents were sampled and analyzed routinely, with a minimum detection limit of 0.047 ng/ml (ppb). Only one set of samples contained measurable amounts of 2,3,7,8-TCDD (Tiernan et al. 1979). No analyses were performed for any other chemical constituents or decomposition products.

This operation also resulted in more than 40,000 steel drums that were still slightly contaminated with Herbicide Orange. These drums were to have been crushed mechanically, then shipped to a steel mill to be melted as steel scrap at a temperature of about 2900° C (Whiteside 1977). No available reports confirm the completion of this procedure. Portions of the ship used in the incineration operation were also contaminated with 86 $\mu g/m^2$ of Herbicide Orange. Subsequent decontamination reduced the concentration by as much as 96 percent (Erk, Taylor, and Tiernan 1979). The decontamination procedure and the fate of the residue are not known (Chemical Week 1978d).

A high-temperature liquid and solid incinerator is being constructed as a mobile unit under an EPA contract (Brugger 1978). Its purpose is to decompose hazardous chemicals such as dioxins, and it is expected to be used to incinerate the dioxin-contaminated sludge now being stored in Verona, Missouri. It may also be used to burn some dioxin-contaminated activated carbon remaining from initial efforts by the U.S. Air Force to remove dioxins from Herbicide Orange by adsorption. This mobile incineration unit is to be equipped with an afterburner and a scrubber for the exhaust gases. It will be able to handle the combustion equivalent of 75 gallons per hour of fuel oils and a solids equivalent of 3.5 tons per hour of dry sand.

In another project, a private partnership plans to convert a tanker for ocean incineration of toxic wastes including 2,4,5-TCP wastes. The ship will be equipped with three 25-ton-per-hour incinerators capable of burning a 10,000-ton load of waste on a week's cruise. The EPA will monitor the test burns during initial operations (Chemical Week 1979g).

Incineration has been suggested for decontamination of the soil and other materials at Seveso, Italy (Commoner 1977; Pocchiari 1978), but local political pressure has killed the idea (Revzin 1979; Chemical Week 1979h). A giant incinerator was to have been built that would have held each furnace charge at 800° to 1000° C for 30 to 40 minutes. Estimates of the amounts of soil to be processed range from 150,000 to 300,000 megagrams. In addition there are huge quantities of contaminated furniture and decaying plants and small animals (about 87,000 in number), which are presently quarantined, awaiting final disposal. Authorities have refused to allow the incinerator to be built because the burning of such massive amounts of dioxin-contaminated debris would take years. Futhermore, the residents and authorities fear that the presence of such an incinerator would result in Seveso becoming the industrial waste dumping ground for all of Italy.

Advanced Incineration Techniques

Two advanced incineration techniques have been studied for the decomposition of toxic substances. Molten-salt combustion consists of burning a contaminated chemical with air below the surface of a liquified inorganic material. Microwave-plasma destruction, although not a true combustion process, converts a mixture of contaminated chemical and oxygen into elemental oxides through the action of microwave radiation.

Molten-Salt Combustion—

The technology of molten-salt combustion has been developed over the past 20 years by Atomics International Division of Rockwell International Corporation (Wilkinson, Kelso, and Hopkins 1978). It has potential application to the destruction of pesticides and hazardous wastes. A schematic of the process is given in Figure 67. A difficulty with developing this system for full-scale practice may be in locating suitable materials of construction.

The molten salt is sodium or potassium carbonate containing 10 percent by weight of sodium sulfate. It is maintained at 800° to 1000°C by application of heating or cooling as needed. When the molten salt is applied to chlorinated hydrocarbon wastes, the carbon and hydrogen in the waste are oxidized to CO_2 and steam, while the chlorine content is changed into sodium chloride. Tests have demonstrated that this bench-scale combustor can achieve virtually complete decomposition (more than 99 percent) of chlorinated hydrocarbons, 2,4-D, chlordane, chloroform, and trichloroethane. The 2,4-D tested was part of an actual waste that contained 30 to 50 percent 2,4-D and 50 to 70 percent bis-ester and dichlorophenol tars. The waste was diluted with ethanol and burned at 830°C. This combustion test destroyed 99.98 percent of the organic materials.

Microwave-Plasma Destruction—

Microwave plasma refers to a partially ionized gas produced by microwave-induced electron reactions with neutral gas molecules (Bailen and Hertzler 1976; Bailen 1978). The ionized gas or plasma is derived from the carrier gas which transports the molecules into the plasma zone (Oberacker and Lees 1977). When oxygen is used as the reactant gas in the plasma, highly reactive atomic oxygen is produced which then rapidly oxidizes organic compounds introduced into the system discharge (Bailen 1978).

A laboratory-scale microwave-plasma reactor with capacity of 1 to 5 g/h, and a pilot-scale reactor with capacity of 430 to 3,200 g/h have been tested by the Lockheed Palo Alto Research Laboratory under a contract from the EPA (Bailen and Hertzler 1976). A schematic diagram of these units is shown in Figure 68. Tests have been conducted with a variety of toxic materials, including two commercial PCB's, Aroclor 1242, and Aroclor 1254. The laboratory-scale reactor converted 99.9 percent of the PCB's into carbon monoxide, carbon dioxide, water, phosgene, and chlorine oxides. The pilot-scale reactor converted at least 99 percent of most materials tested into smaller molecules. One test, however, did not achieve complete destruction and left a black, tarry substance that still contained PCB's.

The pilot reactor was also used in tests with a commercial clay-supported formulation of kepone charged to the reactor as compressed solid material, a 10 percent slurry in water, and a 20 percent slurry in methanol. Conversion of at least 99 percent of each charge material to basic oxides and hydrogen chlorine was achieved in all tests.

Microwave-plasma decomposition has also been used to detoxify U.S. Navy red dye (Bailen 1978). Specific application of this technique to dioxins is not reported, although it has been considered for detoxification of dioxin-contaminated wastes stored in Missouri (Bailen 1977).

PHYSICAL METHODS

Concentration

One approach to disposal or decontamination of toxic substances is by use of techniques that selectively remove toxic constituents from mixtures. Such techniques would reduce the volume of material that must be treated and would offer potential for salvage of useful materials. To date, however, such techniques have presented serious problems because they have been used to concentrate dioxins even with no available means or facilities for disposal of the concentrate.

In at least two instances, quantities of activated carbon heavily contaminated with dioxins are being stored because disposal methods are not available. In this country, extensive pilot-plant studies of carbon adsorption were conducted before the Air Force decided to incinerate Herbicide Orange (Whiteside 1977; Young et al.

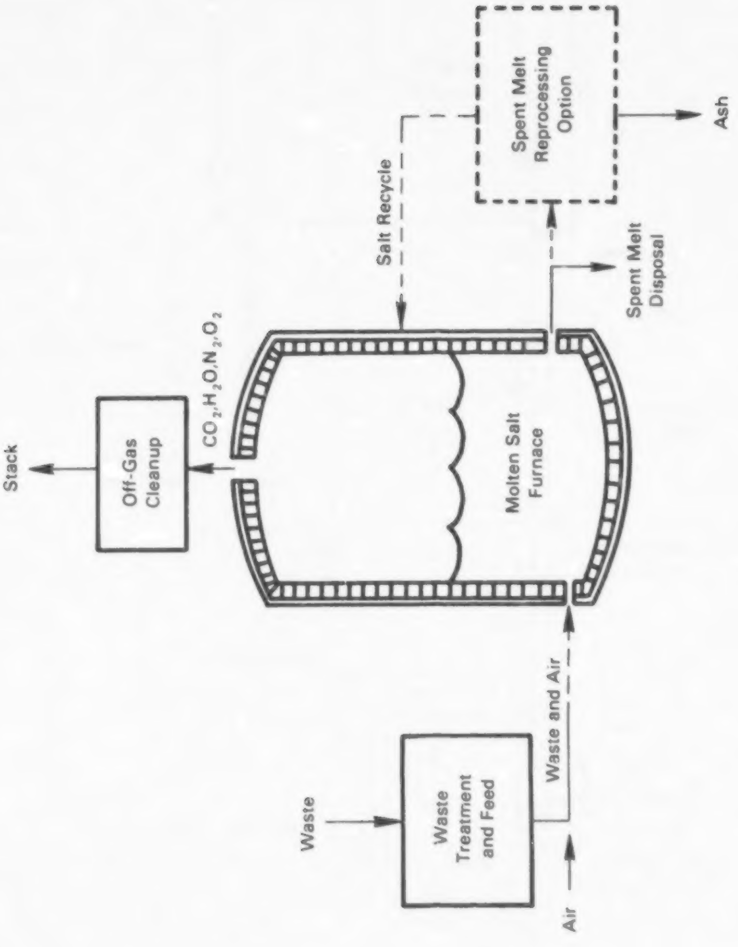

Figure 67. Schematic of molten-salt combustion process.

Source: Wilkinson, Kelso, and Hopkins 1978, as adapted from Atomics International 1975.

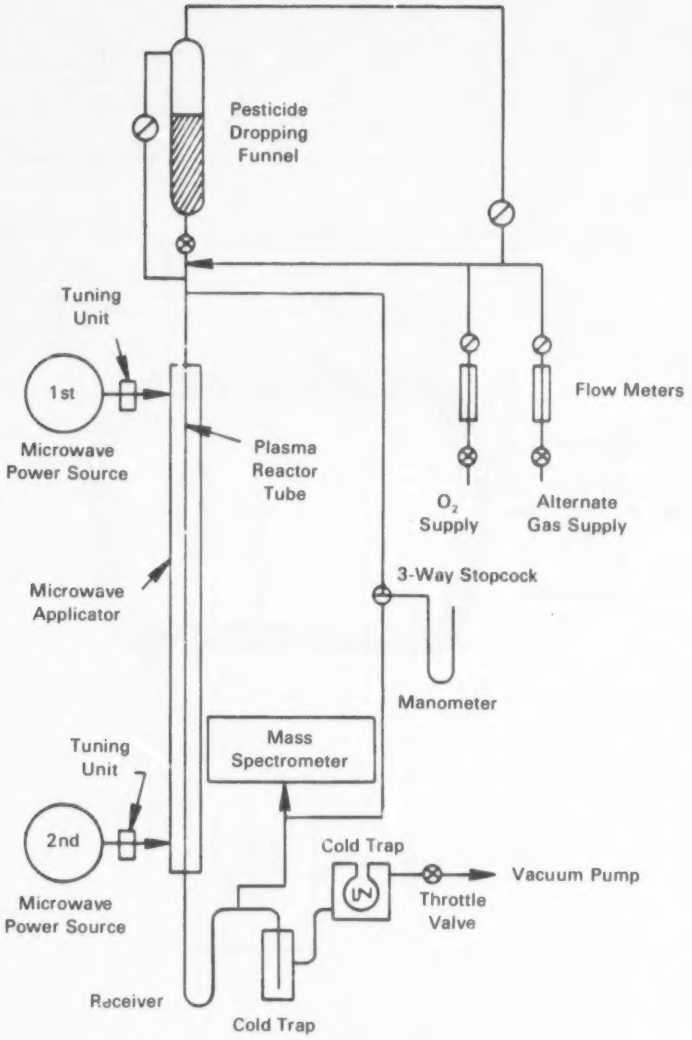

Figure 68. Schematic of microwave plasma system.

Source: Wilkinson, Kelso, and Hopkins 1978, as adapted from Bailen and Hertzler 1976.

1978). Although the reprocessing method was technically and environmentally feasible, it was not possible to demonstrate an acceptable method for safely disposing of the dioxin-laden carbon. The contaminated carbon is now stored on an island in the Pacific. Similarly, Union Carbide of Australia created quantities of dioxin-contaminated carbon in efforts to detoxify 2,4,5-TCP after they became aware of the 2,3,7,8-TCDD problem in 1969 (Chemical Week 1978b; Dickson 1978). This carbon is still stored in steel drums in that country.

Although data are unavailable, activated carbon apparently can adsorb dioxins selectively from chemical mixtures, but the carbon cannot be regenerated. Even after long periods of contact, solvent extraction will not desorb a major portion of the adsorbate. One study evaluated the desorption of phenol from activated carbon with 10 different solvents (Modell, deFilippi, and Krukonis 1978). After 2 hours of continuous extraction, the most effective solvent desorbed only 28 percent of the phenol. A newly proposed technology for regeneration of activated carbon is the use of supercritical fluids (fluids in the region of their critical temperatures and pressures), and in particular supercritical carbon dioxide (Modell, deFilippi, and Krukonis 1978). With one type of activated carbon (Filtrasorb 300, Calgon Corp.), 100 percent desorption was obtained within 3 hours. After the first regeneration, however, adsorption capacity of the carbon is only 50 to 85 percent. It is believed that the initial treatment causes formation of carboxyl, hydroxyl, and carbonyl groups on the surface of the carbon and that their chemical interation with the carbon may lead to irreversible adsorption.

In general, carbon adsorption techniques have not been proven effective for toxics disposal, even if the carbon is to be destroyed by incineration or other methods. After being contaminated with heavy organic chemicals, activated carbon must usually be dried and pulverized prior to incineration to ensure complete destruction. These additional handling steps provide the possibility of fugitive losses.

Bailen and Littauer (1978) are presently investigating the possibility of using microwaves to regenerate spent activated carbon. It is not known whether activated carbon containing dioxins will be evaluated in the study.

Solvent extractions of soil have been shown to be effective in analytical determinations of TCDD's (Tiernan et al. 1980). It has been suggested that solvents such as hexane could be used to extract dioxins from soil by use of equipment similar to that used to extract oil from olive seeds (Commoner 1977). It is not known whether this concentration process has been tested. The use of steam distillation has also been suggested as a means of concentrating dioxins, but no details are available.

Photolysis

The use of light to degrade halogenated aromatic compounds is well established in published literature (Mitchell 1961; Plimmer 1972, 1978a; Rosen 1971; Watkins 1974; Wilkinson, Kelso, and Hopkins 1978). Regarding degradation of dioxins, most studies have been concerned with the effect of sunlight on dioxins released into the environment, as outlined in Section 7. Application of the same principle to detoxify dioxins with artificial light could lead to a means of decontaminating chemical mixtures.

The Velsicol Chemical Corporation has proposed such a photolytic system as an alternative method for disposal of Herbicide Orange (Crosby 1978a, 1978b; Lira 1978). The herbicide mixture would first be hydrolyzed with caustic and converted into butyl alcohol, water, and salts of 2,4-D and 2,4,5-T. Additional butyl alcohol would then be used to extract the dioxins. The butyl alcohol and dioxins would be separated from the phenolic salts and water by decantation, and the organic layer would be irradiated with ultraviolet light. Irradiation would be accomplished in a special reaction apparatus, in which thin films of the liquid are exposed to light from quartz tubes. Although preliminary tests did succeed in destroying 2,3,7,8-TCDD, the process had not been pursued because the toxicity of the resulting decomposition products was unknown and the butyl alcohol would have to be disposed of by incineration or other methods. Further tests of this principle were discontinued.

No other studies of large-scale decomposition of dioxins by use of artificial light have been reported. Some laboratory studies have shown that light does not destroy the structure of dioxins. Under appropriate conditions, light converts the more toxic dioxins to less toxic forms by removing halogen substituents (Crosby 1971). However, Dow Chemical Company has evidence from ultraviolet spectra of irradiated solutions containing dioxins of four or less chlorine atoms that the rings are indeed destroyed (Crummett 1980).

Radiolysis

Radiolysis, an extension of the photolytic method, has been studied experimentally. Gamma rays having properties similar to light have been shown to partially degrade dioxins. As with ultraviolet light, these rays may not totally destroy the dioxin structure, but only remove substituent halogens.

In the most recent series of tests, investigators dissolved 2,3,7,8-TCDD in either ethanol, acetone, or dioxane at a concentration of 100 ng/ml (ppb) and irradiated the solutions at 10^6 rads/h (Chemical Week 1977; Fanelli et al. 1978). They found that 97 percent of the dioxin was degraded after 30 hours, when ethanol was the solvent. Degradation was somewhat slower in the other solvents. All irradiated samples showed the presence of tri-CDD and DCCD.

In 1976, Buser dissolved OCDD in benzene and hexane at a concentration of 25 g/liter and exposed it to gamma radiation. After 4 hours, 80 percent of the OCDD was converted into dioxins with five, six, or seven chlorine substituents. Further degradation did not occur.

Other researchers completed an extended series of tests using gamma radiation of the ionizing type to destroy pesticides (Craft, Kimbrough, and Brown 1975). Significant destruction of single representative compounds such as pentachlorophenol, 2,4,5-T, and 2,4-D was obtained, but no change in PCB's or mixtures of compounds such as Herbicide Orange could be detected. This test series led to the conclusion that because of the inefficiency of radiation in destroying mixtures of pesticides and dioxins, cost would be prohibitive for routine use of this method in waste treatment.

CHEMICAL METHODS

Several chemical techniques have been proposed for the destruction of toxic dioxins. Vertac, Inc., reportedly developed a process for safely destroying its dioxin-containing wastes, but no details are available (Environment Reporter 1979b). Of the five methods outlined in the following paragraphs, only the first two have been tested specifically with dioxins.

Ozone Treatment (Ozonolysis)

The use of ozone is common in chemical waste treatment applications, especially in decomposition of cyanides. It has been used most often in laboratory applications for decomposition of large organic molecules (Wilkinson, Kelso, and Hopkins 1978).

In a recent test, ozone was bubbled through a suspension of 2,3,7,8-TCDD in water and carbon tetrachloride. It was reported that after 50 hours, 97 percent of the 2,3,7,8-TCDD had degraded. In this process, the dioxin apparently is suspended as an aerosol combined with carbon tetrachloride, which facilitates ozone attack (Cavolloni and Zecca 1977).

Another modification of ozone treatment has been developed by Houston Research, Inc. (Wilkinson, Kelso, and Hopkins 1978; Mauk, Prengle, and Payne 1976). Tests with dioxins, however, have not been reported. In this technique, treatment with ozone is combined with ultraviolet irradiation. The light activates organic molecules to a highly energetic state, thereby rendering them more susceptible to ozone attack. When this technique was applied to pentachlorophenol and DDT, these compounds were decomposed into carbon dioxide, water, and hydrochloric acid. A schematic diagram of the apparatus is shown in Figure 69. Two bench-scale reactors of 10- and 21-liter capacity have been constructed (Mauk, Prengle, and Payne 1976).

Although these examples indicate that ozone treatment may be effective for use in dioxin disposal or decontamination, the use of ozone must be combined with some other mechanism that will activate the dioxin and promote the attack of ozone.

Chloroiodide Degradation

In a recently described method, 2,3,7,8-TCDD in contaminated soil is degraded by use of a class of compounds derived from quaternary ammonium salt surfactants and referred to as chloroiodides (Botre, Memoli, and Alhaique 1979). The compounds are formulated in micellar solutions with surfactants that increase the water solubility of the substances. The two derivatives showing the most degradation potential are alkyldimethylbenzyl-ammonium (benzalkonium) chloroiodide and 1-hexadecylpyridinium (cetylpyridinium).

When 2,3,7,8-TCDD in benzene was vacuum evaporated and the residue treated with a cationic surfactant aqueous solution containing benzalkonium chloroiodide, 71 percent of the 2,3,7,8-TCDD decomposed. When cetylpyridinium chloroiodide in cetylpyridinium chloride was used, 92 percent of the 2,3,7,8-TCDD was decomposed. These experiments were performed in absence of light to prevent photolytic degradation.

In a test with soil from Seveso contaminated with 2,3,7,8-TCDD, only about 14 percent was degraded within 24 hours following treatment with benzalkonium chloride. When benzalkonium chloroiodide was added, an additional 38 percent of the 2,3,7,8-TCDD was degraded. Total degradation during this test was 52 percent.

Wet-Air Oxidation

Wet-air oxidation is an accelerated oxidation process performed at high pressure and temperature. Oxidation takes place in an autoclave in which a charge of water and organic material is heated to 150° to 350° C while being pressurized with air to 40 to 140 atmospheres. Three commercial processes of this type are known as the Zimpro, Wetox, and Lockheed processes. They are used for rapid decomposition of sewage sludge, munitions waste, and sulfite liquor from pulp and paper mills. It has been proposed to evaluate the Wetox system for disposal of priority pollutants and other hazardous chemicals (Wertzman n.d.). This might also be an alternative method for disposal of dioxin and dioxin-contaminated materials, but no tests have yet been reported.

Chlorinolysis and Chlorolysis

Although chlorinolysis and chlorolysis were developed primarily to produce chlorinated products from nonchlorinated or less-chlorinated organics, some attention has been focused on their use in waste treatment (Shiver 1976). Chlorinolysis is used primarily to convert hydrocarbons containing one to three carbon atoms into perchloroethylene, trichloroethylene, and carbon tetrachloride (Diamond Alkali Company 1950; U.S. Patent Office 1972). As most often practiced, the process continuously reacts chlorine with ethylene or ethylene

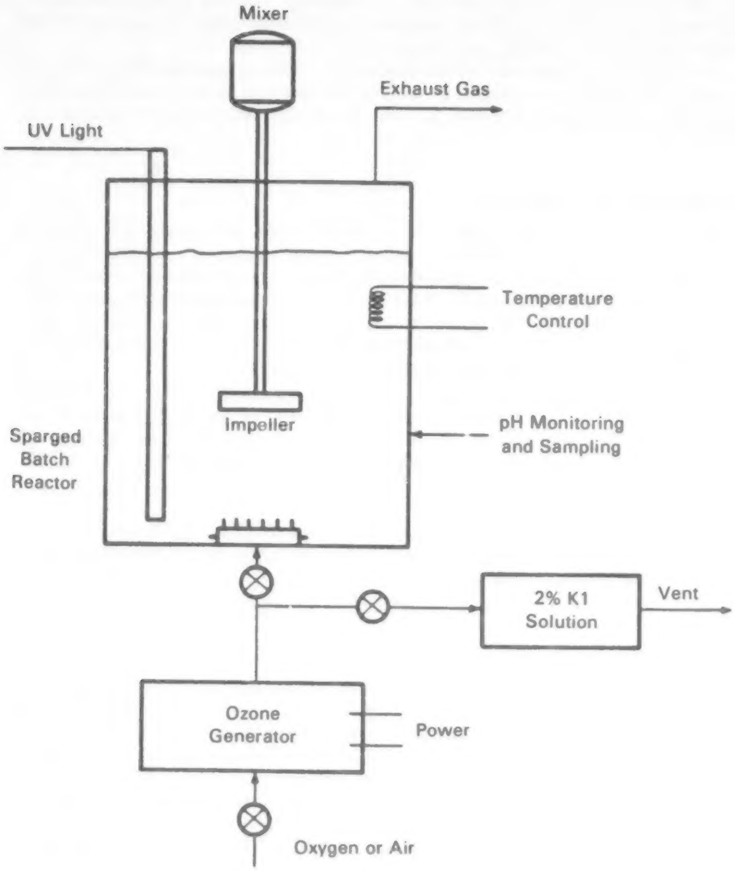

Figure 69. Schematic for ozonation/ultraviolet irradiation apparatus.

Source: Wilkinson, Kelso, and Hopkins 1978, as adapted from Mauk, Prengle, and Payne 1976.

dichloride in a fluid bed catalyst reactor. The process usually creates small amounts of hexachlorobenzene, hexachloroethane, hexachlorobutadiene, tetrachloroethane, and pentachloroethane as side-reaction products.

Chlorolysis, an associated process, is sometimes used to convert the side-reaction products from chlorinolysis into carbon tetrachloride; it can also be used with benzene or its derivatives or with mixtures of chlorinated aromatic or aliphatic compounds. Chlorolysis is a two-stage process in which gaseous feed materials are reacted with chlorine at pressures of 200 to 700 atmospheres and temperatures up to 800°C. No catalyst is used.

In cooperation with the U.S. Department of Agriculture, the Diamond Shamrock Corporation conducted pilot-plant studies to test the stability of 2,3,7,8-TCDD under the severe reaction conditions of chlorolysis (Kearney et al. 1973). Although the results of these studies are not known, the techniques may be applicable to disposal of certain dioxin-contaminated chemicals and might yield marketable products from otherwise waste chemicals.

Catalytic Dechlorination

Catalytic dechlorination is a simple chemical process in which the action of a catalyst reductively dechlorinates an organic compound. The usual catalyst is nickel borohydride, which is prepared in a reaction vessel by mixing sodium borohydride and nickel chloride in a solvent of alcohol. When this solution is mixed with a chlorinated organic chemical, the chlorine atoms are removed from the molecules and hydrogen atoms are substituted (Cooper and Dennis 1978; Dennis 1972; Dennis and Cooper 1975, 1976, 1977; Wilkinson, Kelso, and Hopkins 1978).

Laboratory tests have been conducted with this process to detoxify several commercial pesticides, including DDT's, heptachlor, chlordane, and lindane. Tests with chlorinated dioxins have not been reported. The process does not completely dechlorinate most organic chemicals and would not break down the basic dioxin structure. The reaction occurs rapidly, however, and at room temperature; for these reasons, the process may be of value in decontamination operations or in detoxifying small volumes of toxic dioxins.

Other processes have been used to dechlorinate aromatic compounds, including conventional catalytic hydrogenation with metallic catalysts and hydrogen gas (Dennis and Cooper 1975). In a small-scale laboratory experiment with a catalyst of palladium on charcoal, about 60 percent of a charge of 1,6-DCDD was reduced to unsubstituted dioxin in 1 hour at room temperature and less than 1 atmosphere pressure.

BIOLOGICAL TREATMENT

One of the least expensive techniques for breaking down large organic molecules, and often one of the most effective, is to subject the molecules to the action of microorganisms. Although toxic chemicals are usually degraded slowly in uncontrolled exposure to the environment, more complete and more rapid breakdown can be achieved by controlling the microorganism species and providing specialized environments.

Numerous studies have examined the susceptibility of dioxins, particularly 2,3,7,8-TCDD, to microbial decomposition. Most of the studies have concerned decomposition in the uncontrolled environment, as described in Section 6. Much less attention has been directed to the controlled use of microorganisms. The following paragraphs describe available data on two aspects of the microbial decomposition of dioxins: soil conditioning and biochemical wastewater treatment. A specialized treatment system for toxic wastes is also discussed.

Soil Conditioning

The large area of dioxin-contaminated soil surrounding Seveso, Italy, has stimulated studies of degradation of dioxins by soil microorganisms. Available data indicate that 2,3,7,8-TCDD is resistant to this method of decontamination, although under optimum conditions some slow degradation occurs.

Rates of uncontrolled degradation have been variously measured in two studies. The U.S. Air Force reported the half-life of 2,3,7,8-TCDD at 225 and 275 days (Young et al. 1976). In a separate analysis of the same test data, Commoner (1976b) obtained a half-life of 190 to 330 days. In Seveso, however, Bolton (1978) reported finding no reduction in dioxin levels in the most heavily contaminated zone, and in the less contaminated zone reduction after 400 days was only 25 percent.

Researchers in Zurich, Switzerland, have found that soil-bound 2,3,7,8-TCDD becomes increasingly difficult to recover quantitatively with time (Huetter 1980). This observation may explain the decreasing recoveries of 2,3,7,8-TCDD in soil degradation studies by the U.S. Air Force and others in which the "disappearance" of 2,3,7,8-TCDD with time was interpreted as evidence of biodegradation. Half-lives for 2,3,7,8-TCDD calculated from these studies may not accurately reflect the true persistance of this dioxin in the soil environment.

One proposal for modifying the Seveso soil environment is to use charcoal or activated carbon to hold the dioxins in the soil, then to spread manure on the treated soil to increase the rate of bacterial growth (Young 1976). U.S. Air Force studies have shown, however, that although treatment of this sort increases the number and activity of soil microorganisms, the rate of dioxin degradation is reduced. Apparently, adsorption on charcoal causes the dioxin to be less available to the bacteria. No other proposals to modify the open soil environment have been advanced.

Attempts have been made to inoculate Seveso soil with selected bacteria that might facilitate the breakdown of dioxins. Although initial results appeared promising, subsequent data indicated that the method had not been effective (Commoner 1977). The inoculated species either died out or mutated to a strain that rejected dioxins. In a similar laboratory study of 100 microbial strains that had shown ability to degrade pesticides, only 5 showed any ability to degrade 2,3,7,8-TCDD (Matsumura and Benezet 1973).

Wastewater Treatment Systems

Very little is known concerning the ability of biological or biological/chemical wastewater treatment to remove dioxins.

Dow Chemical Company operates a tertiary treatment system to treat wastewater from its Midland, Michigan, pesticide manufacturing plant (Dow Chemical Company 1978). A two-year program of analysis of grab and composite samples taken from the tertiary effluent stream revealed only one with a detectable amount (0.008 ppb) of TCDD's. In further investigations, six caged fish were placed in the tertiary pond effluent; subsequent analyses showed, in five of the six fish, concentrations of TCDD's ranging from 0.02 to 0.05 ppb in the edible portions and from 0.05 to 0.07 ppb in the whole bodies. These findings, when compared with data on control fish containing no detectable levels of TCDD's, clearly indicate the presence of TCDD's in the tertiary pond effluent.

Data obtained in 1976 from Transvaal, Inc., showed no TCDD's in effluent from the city stabilization ponds, to which Transvaal sends all or part of its plant wastewater effluent (Sidwell 1976b). A sample from the Transvaal plant effluent, however, showed 0.2 to 0.6 ppb of this dioxin. Other than pH adjustment with lime, the effluent apparently undergoes no pretreatment. As previously discussed (p. 173) more recent studies of this site have been reported (Tiernan et al. 1980).

In a third study, sludge was sampled at the outlet of a lagoon holding effluent from a pentachlorophenol manufacturing plant. The sludge was analyzed for

TCDD's, but none was found (U.S. Environmental Protection Agency 1978d). Since this dioxin has never been found as a decomposition product of pentachlorophenol, the negative analysis would be expected. The sludge was not analyzed for hexa-CDD's, hepta-CDD's, or OCDD, the dioxins normally associated with PCP manufacture.

Researchers in Finland have patented a process for purifying wastewaters containing chlorinated aromatics in a biofilter (Salkinoja-Salonen 1979a). The filter consists of a layer of wood bark that contains a strain of bacteria able to degrade the organic compounds (Salkinoja-Salonen 1979 a,b). These bacterial strains were isolated by taking samples of bacteriferous water, mud, or bark residue from water bodies polluted by chlorinated and unchlorinated phenols and aromatic carboxylic acids, then feeding pollutants to the bacterial populations collected. Work is under way to prove the effectiveness of the filter in treating dioxins; its efficacy in treating aromatics such as tri- and tetrachlorophenols has been demonstrated.

Micropit Disposal

A detailed study of biological degradation of pesticides is being conducted by Iowa State University (Rogers and Allen 1978). The apparatus used in the study, shown in Figure 70, consists of a partially buried polyethylene garbage can filled with layers of rock and soil, and flooded with water. The study, sponsored by the U.S. EPA, deals with a variety of pesticides at various concentrations, and with the effects of nutrient additives and aeration. Two organochloride compounds are included among the pesticides being examined, but it is not clear whether the test includes dioxins. Test data are not available.

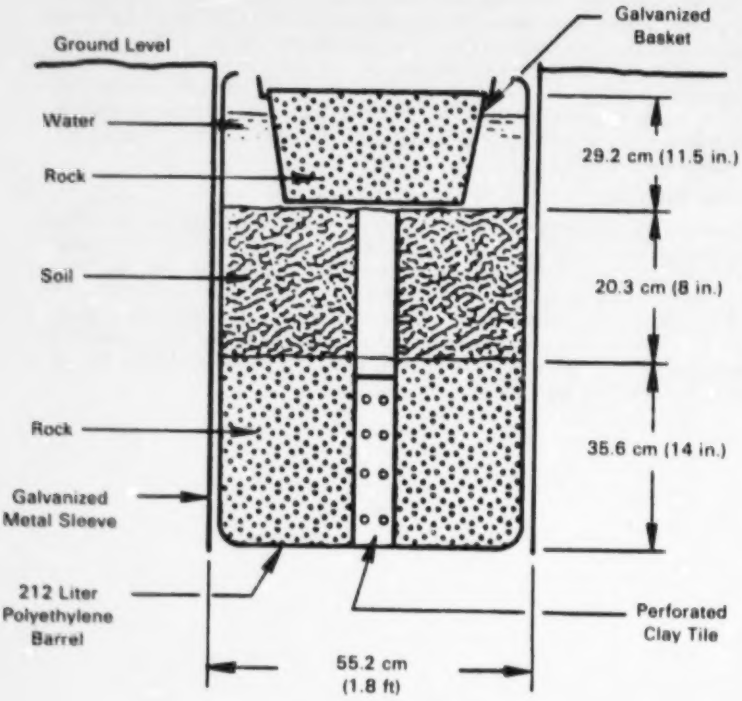

Figure 70. Internal view of pesticide micropit.

Source: Rogers and Allen 1978.

REFERENCES

Ackerman, D.G., et al. 1978. At-Sea Incineration of Herbicide Orange Onboard the M/T *Vulcanus*. EPA-600/2-78-086.

Ahling, B., and A. Lindskog. 1977. Formation of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans during Combustion of a 2,4,5-T Formulation. Chemosphere, 6(8):461–468.

Air/Water Pollution Report. 1978. Around the States—Kansas. June 5, p. 227.

Aitio, A., M. Parkki, and J. Marniemi. 1979. Different Effects of TCDD on Glucuronide Conjugation of Various Aglycones: Studies in Wistar and Gunn Rats. Toxicol. Appl. Pharmacol., 47:55–60.

Albro, P.W. 1978. Effects of TCDD on Lipid Profiles in Tissue of the Fischer Rat. Chon-Biol. Interact., 23(3):315–30.

Albro, P.W. and B.J. Corbett. 1977. Extraction and Clean-Up of Animal Tissues for Subsequent Determination of Mixtures of Chlorinated Dibenzo-*p*-Dioxins and Dibenzofurans. Chemosphere, 7:381.

Allen, J., M.D. 1978. University of Wisconsin, personal communication, August 28.

Allen, J.R. 1967. Light and Electron Microscopic Observations in *Macaca Mulatta* Monkey Fed Toxic Fat. American Journal of Vet. Research, 28:1513–26.

Allen, J.R., J.P. Van Miller, and D.H. Norback. 1975. Tissue Distribution, Excretion, and Biological Effects of [^{14}C]-Tetrachlorodibenzo-*p*-Dioxin in Rats. Fd. Cosmet. Toxicol., 13:501–505.

Allen, J.R., et al. 1975. Morphological Changes in Monkeys Consuming a Diet Containing Low Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxins. Fd. Cosmet. Toxicol., 15:401–410.

Allen, J.R., et al. 1979. Toxicological Responses of Nonhuman Primates to TCDD. Toxicol. Appl. Pharmacol., 48(1):A180.

Ambrose, D. 1971. Gas Chromatography. Van Nostrand, New York.

American Broadcasting Co. 1978. Transcripts of broadcasts aired on July 25 and August 1. 20/20. New York.

American Industrial Hygiene Association Journal. 1980. No Excess in Cancer Deaths Found in Largest Group Ever Studied for Long-Term Effects of Dioxin Exposure. January.

American Wood Preservers Institute. 1977. Memorandum to the Office of Pesticide Programs, U.S. Environmental Protection Agency. Pentachlorophenol: A Wood Preservative Research Triangle Park, North Carolina.

American Wood Preservers Institute Directory. 1977. AE Concepts in Wood Design, No. 17, September-October.

Anaizi, N.H., and J. Cohen. 1979. The Effects of TCDD on the Renal Tubular Secretion of Phenolsulfonphthalein. J. Pharmacol. Exp. Ther., 207(3):748–755.

Anderson, J. 1978. The Poisoning of America. The Washington Post, United Feature Syndicate, Inc., July 15.

Aniline, O. 1973. Preparation of Chlorodibenzo-*p*-Dioxins for Toxicological Evaluation. In: Chlorodioxins—Origin and Fate, E.H. Blair, ed. American Chemical Society, Washington, DC, pp. 126–135.

Arsenault, R.D. 1976. Pentachlorophenol and Contained Chlorinated Dibenzodioxins in the Environment. American Wood Preservers Association.

Auer, C. 1979. EPA Office of Toxic Substances, personal communication with D.R. Watkins, EPA, IERL-Cincinnati, February 26.

Bage, G., E. Cekanova, and K.S. Larsson. 1973. Teratogenic and Embryotoxic Effects of the Herbicides Di- and Trichlorophenoxyacetic Acids (2,4-D and 2,4,5-T). Acta Pharmacol. et Toxicol., 32:408–416.

Bailin, L.J. 1977. Microwave-Plasma Detoxification Process for Hazardous Wastes. EPA, IERL-Cincinnati, EPA Contract No. 68-03-2190, October.

Bailin, L.J. 1978a. Smithsonian Science Information Exchange Notice of Research Project Microwave Regeneration of Activated Carbon. EPA Contract No. 68-03-2660, March 1.

Bailin, L.J. 1978b. Summary Report: Detoxification of Navy Red Dye by Microwave Plasma. EPA-600/2-78-081, June.

Bailin, L.J., and B.L. Hertzler. 1976. Development of Microwave-Plasma Detoxification Process for Hazardous Wastes: Phase I. EPA Contract No. 68-03-2190.

Bailin, L.J., and E.L. Littauer. 1978. Microwave Regeneration of Activated Carbon. EPA, IERL-Cincinnati, Contract No. 68-03-2660, March.

Ball, L.M., and R.S. Chhabra. 1977. Effects of Environmental Pollutants on the Intestinal Absorption of Nutrients. Environmental Health Perspectives, 20:231.

Barbero, R.D. 1978. Response Report: Dioxins in Sludges from the Manufacture of: Trichlorophenol, Pentachlorophenol, and Hexachlorophene. CBC Associates, Inc., Falls Church, Virginia. Unpublished.

Barsotti, D.A., L.J. Abrahamson, and J.R. Allen. 1979. Hormonal Alterations in Female Rhesus Monkeys Fed a Diet Containing TCDD. Bulletin of Environmental Contamination and Toxicology, 21:463–469.

Bartleson, F.D., Jr., D.D. Harrison, and J.B. Morgan. 1975. Field Studies of Wildlife Exposed to TCDD-Contaminated Soils. Air Force Armament Lab. Eglin A.F. Base, Florida.

Baughman, R.W. 1974. Ph.D. Thesis, Harvard University, Boston.

Baughman, R.W., and M. Meselson. 1973a. An Analytical Method for Detecting TCDD (Dioxin): Levels of TCDD in Samples from Vietnam. Environmental Health Perspectives, 5:27–35, September.

Baughman, R.W., and M. Meselson. 1973b. An Improved Analysis for Tetrachlorodibenzo-*p*-dioxin. In: Chlorodioxins—Origin and Fate, E.H. Blair, ed. American Chemical Society, Washington, DC.

Bayer, F. 1910. German Patent No. 223,367. Chemical Abstracts, 4:2981.[4]

Beale, M.G., et al. 1977. Long-Term Effects of Dioxin Exposure. Lancet, 1(8014): 788, April.

Beatty, P.W. 1977. Studies of Metabolism and Possible Mechanisms of Toxicity of TCDD. Thesis, Vanderbilt University, Nashville, TN.

Beatty, P.W., and R.A. Neal. 1976. Induction of DT-diaphorase Activity of Rat Liver by 2,3,7,8-TCDD (Abstract No. 232). Toxicol. Appl. Pharmacol., 37:189.

Beatty, P.W., et al. 1978. Effect of Alteration of Rat Hepatic Mixed Function Oxidase (MFO) Activity on the Toxicity of 2,3,7,8-TCDD. Toxicol. Appl. Pharmacol., 45(2):513–20.

Becker, D. 1973. The Effect of Folate Overdose and of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDBD) on Kidney and Liver Respectively of Rat and Mouse Embryos. Teratology, 8:215.

Benedetto, A.V., and J.S. Taylor. 1978. Porphyria Cutanea Tarda: Update 1978. Cutis, 21:983–88, April.

Berg, G.L., ed. 1975. Farm Chemicals Handbook. Meister Publ. Co., Willoughby, OH.

Berry, D.L., et al. 1978. Lack of Tumor-Promoting Ability of Certain Environmental Chemicals in a Two-Stage Mouse Skin Tumorigenesis Assay. Res. Comm. Chem. Path. and Pharm., 20(1):101–108, April.

Bertoni, G., et al. 1978. Gas Chromatographic Determination of 2,3,7,8-TCDD in the Experimental Decontamination of Seveso Soil by Ultraviolet Radiation. Analytical Chemistry, 50(6):732–735.

Bevenue, A., and H. Beckman. 1967. Pentachlorophenol: A Discussion of Its Properties and Its Occurrence as a Residue in Human and Animal Tissues. Residue Reviews, 19:83–129.

Beynon, J.H. 1960. Mass Spectrometry and Its Applications to Organic Chemistry. Elsevier, Amsterdam.

Blair, E.H., K.C. Kaner, and E.E. Kenaga. 1963. Synthesis and Insecticidal Activity of *O*-methyl *O*-(2,4,5-Trichlorophenyl) Phosphoramidothioates and Related Compounds. J. Agric. Food Chem., 11(3):237–240.

Blair, E.H., ed. 1973. Chlorodioxins—Origin and Fate. American Chemical Society, Washington, DC.

Blair, G.H. 1979. The Safety of 2,4,5-T. Science, 206:1135–6, December.

Blitz, H. 1904. Ueber die Oxydirende Chlorirung des *o*-Oxy-benzaldehyds und des *p*-Oxy-benzaldehyds. Ber., 27:4009.

Blum, B. 1979. U.S.EPA Deputy Administrator, Press Conference Statement: Emergency Action to Stop Spraying of the Herbicides 2,4,5-T and Silvex. Also U.S. EPA Environmental News release, March 1.

Boer, F.P., et al. 1971. X-ray Diffraction Studies of Chlorinated Dibenzo-*p*-Dioxins. In: Chlorodioxins—Origin and Fate, E. Blair, ed. American Chemical Society, Washington, DC, pp. 14–15.

Bolton, L. 1978. Seveso Dioxin: No Solution in Sight. Chem. Eng., 85(22):78, October 9.

Bonaccorsi, A., R. Fanelli, and G. Tognoni. 1978. In the Wake of Seveso. Ambio, 7(5–6):234–239.

Boobis, A.R. 1979. Effects of Microsomal System Inducers in Vivo and Inhibitors in Vitro on the Covalent Binding of Benzo(a) pyrene Metabolites to DNA Catalyzed by Liver Microsomes from Genetically Responsive and Nonresponsive Mice. Biochemical Pharmacology, 28(1):111–122.

Botre, C., A. Memoli, and F. Alhaique. 1978. TCDD Solubilization and Photodecomposition in Aqueous Solutions. Environmental Science and Technology, 12(3):335–336.

Botre, C., A. Memoli, and F. Alhaique. 1979. On the Degradation of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) by Means of a New Class of Chloriodides. Environmental Science and Technology, 13(2):228–231.

Bowes, G.W., et al. 1973. The Search for Chlorinated Dibenzofurans and Chlorinated Dibenzodioxins in Wildlife Populations Showing Elevated Levels of Embryonic Death. Environmental Health Perspectives, 5:191–8, September.

Bradlaw, J.A. 1979. Induction of Enzyme Activity in Cell Culture: A Rapid Screen for Detection of Planar Polychlorinated Organic Compounds. J. Assoc. Offic. Anal. Chem., 62:904–916.

Brugger, J.E. 1978. Use of Mobile Incinerator to Dispose of *p*-Dioxin. Written communication to K.Q. Camin, Regional Administrator, EPA Region VII, from U.S. EPA, OHMSB, IERL-Ci, June 16.

Buser, H.R. 1975. Polychlorinated Dibenzo-*p*-Dioxin: Separation and Identification of Isomers by Gas Chromatography-Mass Spectrometry. J. Chromatography, 114:95–108.

Buser, H.R. 1976a. High Resolution Gas Chromatography of Polychlorinated Dibenzo-*p*-Dioxins and Dibenzofurans. Anal. Chem., 48:1553–1557.

Buser, H.R. 1976b. Preparation of Qualitative Standard Mixtures of Polychlorinated Dibenzo-*p*-Dioxins and Dibenzofurans by Ultraviolet and γ-Irradiation of the Octachloro Compounds. J. Chromatography, 129:303–7.

Buser, H.R. 1977. Determination of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Environmental Samples by High-Resolution Gas Chromatography and Low-Resolution Mass Spectrometry. Anal. Chem., 49:918–922.

Buser, H.R. 1978. Polychlorinated Dibenzo-*p*-Dioxins and Dibenzofurans: Formation, Occurrence and Analysis of Environmentally Hazardous Compounds. Department of Organic Chemistry, University of Umea, Sweden, and Swiss Federal Research Station, Waedenswil, Switzerland, pp. 9–21.

Buser, H.R. 1979a. Formation and Identification of Tetra- and Pentachlorodibenzo-*p*-Dioxins from Photolysis of Two Isomeric Hexachlorodibenzo-*p*-Dioxins. Chemosphere, 4:251–257.

Buser, H.R. 1979b. Formation of Polychlorinated Dibenzofurans (PCDF's) and Dibenzo-*p*-Dioxins (PCDD's) from the Pyrolysis of Chlorobenzenes. Chemosphere, 6:415–424.

Buser, H.R., and H.P. Bosshardt. 1974. Determination of 2,3,7,8-Tetrachlorodibenzo 1,4 Dioxin at Parts-Per-Billion Levels in Technical Grade 2,4,5-Trichlorophenoxyacetic Acid, in 2,4,5-T Alkyl Ester, and 2,4,5-T Amine Salt Herbicide Formulations by Quadrupole Mass Fragmentography. J. Chromatography, 90:71–77.

Buser, H.R., and H.P. Bosshardt. 1976. Determination of Polychlorinated Dibenzo-*p*-Dioxins and Dibenzofurans in Commercial Pentachlorophenols by Combined GC-MS. Journal of the AOAC, 59(3):562–569.

Buser, H.R., and H.P. Bosshardt. 1978. Polychlorinated Dibenzo-*p*-Dioxins, Dibenzofurans, and Benzenes in the Fly Ash of Municipal and Industrial Incinerators. Mitt. Geb. Lebensmittelsunters Hyg., 69(2):191–199.

Buser, H.R., and C. Rappe. 1978. Identification of Substitution Patterns in Polychlorinated Dibenzo-*p*-Dioxins (PCDD's) by Mass Spectrometry. Chemosphere, 7(2):199–211.

Buser, H.R., H.P. Bosshardt, and C. Rappe. 1978. Identification of Polychlorinated Dibenzo-*p*-Dioxin Isomers Formed in Fly Ash. Chemosphere, 7(2):165–172.

Buu-Hoi, N.P. 1971a. Preparation, Properties, and Identification of Dioxin (2,3, 7,8-Tetrachlorodibenzo-*p*-Dioxin) in the Pyrolyzates of Defoliants Based on 2,4,5-Trichlorophenoxyacetic Acid and Its Esters and in Contaminated Plants. C. R. Acad. Sci., Ser. D 273:708.

Buu-Hoi, N.P., et al. 1971b. Properties Canceramimetiques de la Tetrachloro 2,3,7,8 Dibenzo-*p*-Dioxins. C. R. Acad. Sci. (Paris), 272:1447–1450.

Buu-Hoi, N.P., et al. 1972. Organs as Targets of "Dioxin" (2,3,7,8-TCDD) Intoxication. Naturwissenschaften, 59:174.

Cadogan, J., J. Sharp, and M. Traftles. 1974. Evidence for 1,2-Ketocarbenes in Thermolysis of Sodium *o*-Halogenophenoxides and for Sodium *o*-Bromobenzenethiolates. J. Chem. Soc., Chem. Commun., 900.

Campbell, K. 1979. Effect of Exposure to Chemical Contaminants on Susceptibility to Infection by Pathogenic Organisms. Tox. Research Proj. Directory, 04:05.

Carlstedt-Duke, J.M. 1979. B. Tissue Distribution of the Receptor for TCDD in the Rat. Cancer Research, Issue 8, 39:3172–3176.

Carreri, V. 1978. Review of the Events which Occurred in Seveso. In: Dioxin: Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallaro, and G. Galli, eds. SP Medical and Scientific Books. Spectrum Publications, Inc., New York, pp. 1–4.

Carter, C.D., et al. 1975. Tetrachlorodibenzodioxin: An Accidental Poisoning Episode in Horse Arenas. Science, 188(4189):738–740.

Cassito, L., and P. Magni. 1977. Method for Emission Control at the Proposed Seveso Incinerating Plant Using Gas Chromatography and Mass Fragmentography. Inquinamento, 19(5):33–38.

Cattabeni, F., et al. 1978. Dioxin: Toxicological and Chemical Aspects. SP Medical and Scientific Books. Spectrum Publications, Inc., New York, pp. 1–4.

Cavolloni, L., and L. Zecca. 1977. La Decomposizione del TCDD Mediante Ozono. Medicina Termale e Climatologia, 34:73–74.

CEFIC. 1978. Biodegradation Status Report. Safety of Chemicals Committee, Biodegradation Task Force, Brussels, February, p. 9.

Chem. and Eng. News. 1974a. Vietnam Foliage Hit Hard by Herbicides. 52(9):6–7, March 4.

Chem. and Eng. News. 1974b. War Herbicide Report Stirs Controversy. 52(10): 18–19, March 11.

Chem. and Eng. News. 1978. Old Landfill Site Poses Health Problems. August 7, p. 6.

Chemical Engineering. 1978. British Plant Shut Because of Health Risk. September 11, p. 107.

Chemical Regulation Reporter. 1978. Pentachlorophenol: Study Group Advises Using Controls to Reduce Dioxin Impurity Levels. Vol. 2, No. 1, April 7, pp. 6–7.

Chemical Regulation Reporter. 1979a. Reports on Bioassays of Three Chemicals Available from National Cancer Institute. March 2, p. 216.

Chemical Regulation Reporter. 1979b. Hooker Chemicals Installing Toxic Controls at Montague, Michigan, Site. June 22, pp. 457–458.

Chemical Regulation Reporter. 1979c. Ban on All Remaining Uses of 2,4,5-T, Silvex to be Considered at Hearings. July 13, p. 529–30.

Chemical Regulation Reporter. 1980a. NIOSH Finds Dioxin, Carcinogens in Plant Dust Samples near Landfill. January 11, p. 1593.

Chemical Regulation Reporter. 1980b. Dioxins: EPA Finds No Detectable Levels of TCDD in Mother's Milk Samples. January 18, p. 1620.

Chemical Week. 1977. Detoxifying Dioxin. November 23, p. 17.

Chemical Week. 1978a. Dioxin Lingers On. April 12.

Chemical Week. 1978b. Dioxin Down Under. May 10.

Chemical Week. 1978c. Checking Dioxin. May 17.

Chemical Week. 1978d. 2,4,5-T Under Fire. June 14.

Chemical Week. 1978e. Scrubdown for Dioxin. June 21.

Chemical Week. 1979a. Hooker Dumpsites May Pose Dioxin Threat. 124(1):16, January 3.

Chemical Week. 1979b. Faulty Reporting of Seveso Birth Defects. 124(9), February 28.

Chemical Week. 1979c. More Agent Orange Suits Filed in Chicago; Still Others Will Follow. 124(9), February 28.

Chemical Week. 1979d. Still More Hassles for Hooker. April 25, p. 23.

Chemical Week. 1979e. Dioxin is Found in Cleanup Worker's Blood. May 23.

Chemical Week. 1979f. Discovery of Dioxin at Montague Could Impede Accord on Hooker Wastes. June 6, p. 18.

Chemical Week. 1979g. Global Marine Will Burn Chemical Wastes at Sea. July 11.

Chemical Week. 1979h. Seveso Cleanup Still Not Solved. July 18.

Chemical Week. 1979i. Suits Boost Claims for Dioxin-Spill Damage. July 25.

Chem. Sources-U.S.A. 1975. Directories Publishing Co., Inc., Flemington, NJ.

Chulkov, Y.I., V. Parini, and B. Staroselets. 1937. The Action of Chlorine on Phenol in Alkaline Solution and a Possible Method for Preparation of Chloranil. Chemical Abstracts, 31:4967.

Ciaccio, E.I. 1979. Dioxin Contamination. Chemical and Engineering News, April 16, p. 3.

Cincinnati Enquirer. 1978a. Chemical Dumps Proving Hazardous. August 6.

Cincinnati Enquirer. 1978b. Residents near Canal Fear Poisoning. August 6.

Cincinnati Enquirer. 1978c. Grass-Roots Protest Forming over Spraying of Herbicide. August 20, p. J-6.

Cincinnati Enquirer. 1979. Bayou Closed by Herbicide. August 23.

Cleary, T.F. 1971. Production of 2,3-Methylenebis (3,4,6-Trichlorophenol). Centerchem., Inc., September 21.

Cocucci, S., et al. 1979. Absorption and Translocation of Tetrachlorodibenzo-*p*-Dioxin by Plants from Polluted Soil. Experientia, 35(4):482–484.

Colledge, C. 1978. U.S. EPA Technical Services Div., personal communication, August 21.

Collins, T.F.X., and C.H. Williams. 1971. Teratogenic Studies with 2,4,5-T and 2,4-D in the Hamster. Bulletin of Environmental Contamination and Toxicology, 6(6):559–567.

Commoner, B. 1976. Reliability of Bacteria Mutagenesis Techniques to Distinguish Carcinogenic and Noncarcinogenic Chemicals. EPA-600/1-76-022, 1-103.

Commoner, B. 1977. Seveso: The Tragedy Lingers On. Hospital Practice, pp. 31, 33.

Commoner, B., and R.E. Scott. 1976a. Accidental Contamination of Soil with Dioxin in Missouri: Effects and Countermeasures. Center for the Biology of Natural Systems. Washington University, St. Louis, MO.

Commoner, B., and R.E. Scott. 1976b. U.S.A.F. Studies on the Stability and Ecological Effects of TCDD (Dioxin): An Evaluation Relative to the Accidental Dissemination of TCDD at Seveso, Italy. Center for the Biology of Natural Systems, Washington University, St. Louis, MO.

Cookson, C. 1979. "Emergency" Ban on 2,4,5-T Herbicide in U.S. Nature 278:108-109, March 8.

Cooper, J.J., and W.H. Dennis, Jr. 1978. Catalytic Dechlorination of Organochlorine Compounds IV: Mass Spectral Identification of DDT and Heptachlor Products. Chemosphere, 4:229-305.

Cosmetic, Toiletry, and Fragrance Association, Inc. 1977. CTFA Cosmetic Ingredient Dictionary, 2nd ed., Washington, DC.

Courtney, K.D. 1970. Teratogenic Evaluation of 2,4,5-T. Science, 168:864-866, May.

Courtney, K.D. 1976. Mouse Teratology Studies with Chlorodibenzo-*p*-Dioxins. Bulletin of Environmental Contamination and Toxicology, 16(6):674-681.

Courtney, K.D., and J.A. Moore. 1971. Teratology Studies with 2,4,5-Trichlorophenoxyacetic Acid and 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Toxicol. Appl. Pharmacol., 20:396-403.

Courtney, K.D., M.T. Ebron, and A.W. Tucker. 1977. Distribution of 2,4,5-Trichlorophenoxyacetic Acid in the Mouse Fetus. Tox. Letters, 1:103-108.

Courtney, K.D., et al. 1978. Metabolic Studies with TCDD (Dioxin)-Treated Rats. Alch. Environ. Contam. Toxicol., 7:385-396.

Cox, J.M., B.A. Wright, and W.W. Wright. 1965. Thermal Degradation of Poly (Phenylene Oxides). J. Appl. Polymer Sci., 9:513-522.

Craft, T.F., R.D. Kimbrough, and C.T. Brown. 1975. Radiation Treatment of High-Strength Chlorinated Hydrocarbon Wastes, U.S. EPA-660/2-75-017.

Creso, E., et al. 1978. Neuropsychopharmacological Effect of TCDD. Boll-Soc. Ital. Biol. Sper., 54:1512-1516.

Crosby, D.G. 1969. Experimental Approaches to Pesticide Photodecomposition. Residue Reviews, 25:1-12.

Crosby, D.G. 1978a. Conquering the Monster—The Photochemical Destruction of Chlorodioxins. In: Proceedings of American Chem. Soc. Symposium on Disposal and Decontamination of Pesticides, pp. 1-12.

Crosby, D.G. 1978b. University of California, Davis, personal communication, August 21.

Crosby, D.G., and A.S. Wong. 1973. Photochemical Generation of Chlorinated Dioxins. Chemosphere, 5(5):327-332.

Crosby, D.G., and A.S. Wong. 1977. Environmental Degradation of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD). Science, 195:1337-1338, March 25.

Crosby, D.G., K.W. Moilanen, and A.S. Wong. 1973. Environmental Generation and Degradation of Dibenzodioxins and Dibenzofurans. Environmental Health Perspectives, 5:259-265, September.

Crosby, D.G., et al. 1971. Photodecomposition of Chlorinated Dibenzo-*p*-Dioxins. Science, 73:748–749, August 20.

Crossland, J., and K. Shea. 1973. The Hazard of Impurities. Environment, 15(5): 35–38, June.

Crow, K.D. 1977. Effects of Dioxin Exposure. Lancet, 8028:82–83, July 9.

Crow, K.D. 1978. Chloracne—An Up-To-Date Assessment. Ann. Occup. Hyg., 21(3):297–8.

Crummett, W.B. 1980. Personal communication to D.R. Watkins.

Crummett, W.B., and R.H. Stehl. 1973. Determination of Chlorinated Dibenzo-*p*-Dioxins and Dibenzofurans in Various Materials. Environmental Health Perspectives. 5:15–25, September.

Cullinane, N.M., and C.G. Davies. 1936. Synthesis of Some Heterocyclic Compounds. Rec. Trav. Chim., 55:881.

Czeizel, E., and J. Kiraly. 1976. Chromosome Exam in Workers Producing Klounal and Buvinol in the Development of a Pesticide as a Complex Scientific Task, L. Banki, ed. Medicina, Budapest, pp. 239–256.

Dal Nogare, S., and R.S. Juvet. 1962. Gas Chromatography: Theory and Practice. Wiley-Interscience, New York.

Davring, L., and M. Summer. 1971. Cytogenetic Effects of 2,4,5-Trichlorophenoxyacetic Acid on Oogenesis and Early Embryogenesis in *Drosophila Melanogaster*. Hereditas, 68:115–122.

Deinaer, M., et al. 1979. Isolation and Identification of Suspected Toxicants in Pentachlorophenol. Presented before the Division of Environmental Chemistry, American Chemical Society, Honolulu, HI, April.

Denivelle, L., R. Fort, and P.V. Hai. 1960. Octachloro- and Octabromodibenzo-*p*-Dioxins and Decachloro- and Decabromodiphenyl Ether. Bull. Soc. Chim. France, 1538.

Denivelle, L., R. Fort, and V.H. Pham. 1959. Structural Study on Some Pentachloro (pentachlorophenoxy) phenols Derived Therefrom. Compt. rend., 248, 2766.

Denivelle, L., R. Fort, and V.H. Pham. 1960. Octachloro- and Octabromodibenzo-*p*-Dioxins and Decachloro- and Decabromodiphenyl Ether. Bull. Soc. Chim. France, 1538.

Dennis, W.H., Jr. 1972. Methods of Chemical Degradation of Pesticides and Herbicides—A Review. NTIS AD-752 123.

Dennis, W.H., Jr., and W.J. Cooper. 1975. Catalytic Dechlorination of Organochlorine Compounds. I. DDT. Bulletin of Environmental Contamination and Toxicology, 14(6):738–744.

Dennis, W.H., Jr., and W.J. Cooper. 1976. II. Heptachlor and Chlordane. Bulletin of Environmental Contamination and Toxicology, 16(4):425–430.

Dennis, W.H., Jr., and W.J. Cooper. 1977. III. Lindane. Bulletin [illegible] vironmental Contamination and Toxicology. 18(1):57–59.

Diamond Alkali Company. 1952. Improvements in or Relating to the Preparation of Chlor-Substituted Ethylene Derivatives. The Patent Office. Patent No. 673,565, London, June 23.

Dickson, J.P. 1978. Written communication to D. Watkins, U.S. EPA, IERL-Ci, from State Pollution Control Commission, Sydney, Australia.

DiGiovanni, J., et al. 1977. (TCDD) and Aroclor 1254 in the Two-Stage System of Mouse Skin Carcinogenesis. Bulletin of Environmental Contamination and Toxicology, 18(5):552–57.

DiGiovanni, J., et al. 1979. 2,3,7,8-TCDD: Potent Anticarcinogenic Activity in CD-1 Mice. Biochem. and Biophys. Res. Comm., 86(3):577–84, February.

Doedens, J.D. 1964. Chlorophenols. Kirk-Othmer, 2nd ed. Vol. 5, pp. 325–338.

Dombrowski, D., ed. 1978. Toxic Materials News, 5(33):236, August 16, Silver Springs, MD.

Dorman, L.F. 1978. President of American Wood Preservers Inst., personal communications, August 22 and September 5.

Dow Chemical Company. 1978. The Trace Chemistries of Fire—A Source of and Routes for the Entry of Chlorinated Dioxins into the Environment. The Chlorinated Dioxin Task Force, the Michigan Division, Dow Chemical, U.S.A.

Dow Chemical Company. 1980. Science, in press.

Duqois, P., et al. 1967. Acne, Chlorique Collective et Accidentelle d'un Type Nouveau. Bull. Soc. Franc. Derm. Syph., 75:260–261.

Duvall, D.S., and W.A. Rubey. 1976. Laboratory Evaluation of High Temperature Destruction of Kepone and Related Pesticides. Tech. Rep. UDRI-TR-76-21. University of Dayton Research Institute. EPA-600/2-76-299.

Duvall, D.S., W.A. Rubey, and J.A. Mescher. 1978. Laboratory Characterization of the Thermal Decomposition of Hazardous Wastes. In: Proceedings of the Fourth Annual Research Symposium—Land Disposal of Hazardous Wastes. EPA-600/9-78-016.

Eaton, D.L. 1979a. Alterations in Hepatic Transport Systems in Isolated Rat Hepatocytes after Treatment with Microsomal Enzyme Induced. Toxicol. Appl. Pharmacol., 48(1):A187.

Eaton, D.L. 1979b. Characteristics of Hepatic Transport Systems in Isolated Rat Hepatic Parenchynal Cells. Diss. Abstract. Int. B., 39(11):5337.

Edmunds, J.W., D.F. Lee, and C.M.L. Nickels. 1973. Pestic. Sci., 4:101.

Elovaara, E., et al. 1977. Neurochemical Effects of 2,3,7,8-TCDD in Wistor and Gunn Rats. Res. Commun. Chem. Pathol. Pharmacol., 18(3):487–494.

Elvidge, D.H. 1971. The Gas-Chromatographic Determination of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in 2,4,5-Trichlorophenoxyacetic Acid ("2,4,5-T"), 2,4,5-T Esters and 2,4,5-Trichlorophenol. Analyst, 96:721–727.

Ensign, T., and M. Uhi. 1978. Dioxin: Uncovered by Accident, the Number of Cases is Rising Dramatically. In These Times, July 19–25, p. 16.

Environment Reporter. 1978. EPA to Investigate Possible Link Between Herbicide Use, Miscarriages. 9(16):670–671, August 18.

Environment Reporter. 1979a. EPA Cites Miscarriage Correlation in Imposing Emergency Ban on 2,4,5-T. March 9, p. 2074-S.

Environment Reporter. 1979b. Arkansas—Administrative Order Requires Cleanup of Dioxin Wastes at Vertac, Inc., Site. June 22.

Epstein, S.S. 1970. A Family Likeness. Environment, 12(6):16–25.

Erk, S.D., M.L. Taylor, and T.O. Tiernan. 1978. Environmental Monitoring in Conjunction with Incineration of Herbicide Orange at Sea. Proceedings of the 4th National Conference and Exhibition on Control of Hazardous Material Spills, pp. 226–231.

Erk, S.D., M.L. Taylor, and T.O. Tiernan. 1979. Determination of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Residues on Metal Surfaces by GC-MS. Chemosphere 8(1):7-14.

Ernst and Ernst. 1977. Wood Preservation Statistics 1976. In: AWPA Proceedings, pp. 181-217.

Fadiman, A. 1979. A Poisoned Town. Life Magazine, September, pp. 43-46, 49.

Faith, R.E., and M.I. Luster. 1977. Modulation of Immune Function by Chemicals of Environmental Concern. Environmental Health Perspectives, 20:245.

Fanelli, R., et al. 1978. Degradation of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Organic Solvents by Gamma Ray Irradiation. Experientia, 34(9):1126-1127, September 9.

Fanelli, R., et al. 1979. Studies of TCDD Levels in Animals Living in the Seveso Area. Presented in Rome at the Meeting of the Expert Committee of the National Academy of Sciences, March 5-6.

Fanelli, R., et al. 1980a. Presence of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Wildlife Living near Seveso, Italy: A Preliminary Study. Institute de Ricerche Farmacologiche "Mario Negri," Milan, Italy. Prepublication copy.

Fanelli, R., et al. 1980b. 2,3,7,8-TCDD Levels in Cow's Milk from the Contaminated Area of Seveso. Mario Negri Institute for Pharmacological Research, Milan, Italy. Prepublication copy.

Fara, G.M. 1977. Seveso—Studies in Teratogenic and Other Chronic Effects of Chemical Pollutants Following an Accident in a Chemical Plant. Teratology, 16:365.

Farbenind, I.G. 1934. Diaryl Sulfides. Chemical Abstracts, 28:179.

Federal Working Group on Pest Management. 1974. Occupational Exposure to Pesticides. Washington, DC.

Fee, D.C., et al. 1975. Analytical Methodology for Herbicide Orange. Volume II. Determination of USAF Stocks. Aerospace Research Laboratories Technical Report TR75-0110 Volume II.

Ferguson, T.L., et al. 1975. Determination of Incinerator Operating Conditions Necessary for Safe Disposal of Pesticides. EPA-600/2-75-041.

Field, B., and C. Kerr. 1979. Herbicide Use and Incidence of Neural Tube Defects. Lancet, 1(8130):1341-1342.

Firestone, D. 1973. Etiology of Chick Edema Disease. Environmental Health Perspectives, 5:59-66.

Firestone, D. 1977. The Determination of Polychlorodibenzo-*p*-Dioxin and Polychlorodibenzofurans in Commercial Gelatins by Gas-Liquid Chromatography. J. Agric. Food Chem., 25(6):1275-1280.

Firestone, D. 1978. The 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Problem: A Review. In: Chlorinated Phenoxy Acids and Their Dioxins: Mode of Action, Health Risks, and Environmental Effects, C. Ramel, ed. Ecol. Bull. (Stockholm).

Firestone, D., et al. 1972. Determination of Polychlorodibenzo-*p*-Dioxins and Related Compounds in Commercial Chlorophenols. Journal of the AOAC, 55(1):85-92.

Fishbein, L. 1973. Mutagens and Potential Mutagens in the Biosphere. I. DDT and Its Metabolites, Polychlorinated Biphenyls, Chlorodioxins, Polycyclic Aromatic Hydrocarbons, Haloethers. The Science of the Total Environment, 4:305.

Fishbein, L. 1978. Overview of Potential Mutagenic Problems Posed by Some Pesticides and Their Trace Impurities. Environmental Health Perspectives, 27:125–131.

Fowler, B. A., G. E. R. Hood, and G. W. Lucier. 1975. Tetrachlorodibenzo-*p*-Dioxin Induction of Renal Microsomal Enzyme Systems. Toxicol. Appl. Pharmacol., 33:176–177.

Fox, J.L. 1979. Research Solving Body's Detoxifying System. Chem. and Eng. News, 24–25, June 6.

Fries, G., and Marrow. J. Agrio. Fd. Chem. 23:265–269. 1975.

Frejka, J., B. Sefranek, and J. Zika. 1937. New Method of Preparing Some Halogenated Derivatives of Dihydroxydi-*o*-Phenylene Dioxide. Collection Czech. Commun., 9:238. Chemical Abstracts, 31:7074.

Frigerio, A. 1978. The Seveso Case: TCDD in Animals from Contaminated Areas. Methodol. Surv. Biochem., 7:161–166.

Fujita, E., and N. Gota. 1955. Synthesis of Diphenylene Dioxide Derivatives. XXII. Synthesis of 7,8-Phenylenedioxyquinoline. J. Pharm. Soc. Japan, 75:28. Chemical Abstracts, 50:1021, 1956.

Fujita, E., et al. 1956. Synthesis of Diphenylene Dioxide (Dibenzo-*p*-Dioxin) Derivatives. XXIII. Synthesis of Phenylene-Dioxyquinolines (Benzo-*p*-Dioxinoquinolines). J. Pharm. Soc. Japan, 76:1097. Chemical Abstracts 51:2791, 1957.

Fuller, J.G. 1977. The Poison That Fell from the Sky. Reader's Digest, August, pp. 192–236.

Galet, A. 1952. The Preparation of 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T). J. Am. Chem. Soc., 74:3890.

Galston, A.W. 1975. The Ungreening of South Vietnam. Natural History, 83(6):10,12,14.

Galston, A. W. 1979. Herbicides: A Mixed Blessing. Bioscience, 29(2):85–89, February.

Gasiewicz, T. A., and R. A. Neal. 1978. Tissue Distribution and Excretion of 2,3,7,8-TCDD and Effects upon Clinical Chemical Parameters in the Guinea Pig. Fed. Proc. Fed. Am. Soc. Exp. Biol., 37(3):501.

Gebefuigi, I., R. Baumann, and F. Korte. 1977. Photochemical Degradation of 2,3,7,8-TCDD under Simulated Environmental Conditions. Naturwissenschaften, 64(9):486–487.

General Accounting Office. 1979. Health Effects of Exposure to Herbicide Orange in South Vietnam Should Be Resolved. Report by the Comptroller General, CED-79-22, April 6.

Getzendaner, M. D., N. H. Mahle, and H. S. Higgins. 1977. Search for the Presence of 2,3,7,8-Trichlorodibenzo-*p*-Dioxin in Bovine Milk. Bulletin of Environmental Contamination and Toxicology, 18:2.

Gilman, H., and J. Dietrich. 1957. Halogen Derivatives of Dibenzo-*p*-Dioxin. J. Am. Chem. Soc., 79:1439.

Gilman, H., and J. Dietrich. 1958. Bromomito and Related Derivatives of Dibenzo-*p*-Dioxins. J. Am. Chem. Soc., 80:366.

Goldmann, P. J. 1972. Extremely Severe Acute Chloracne Due to Trichlorophenol Decomposition Products. Industrial Medicine, Social Medicine, Industrial Hygiene, 7(1):12–18, January.

Goldmann, P. J. 1973. Schwerste Acute Chloracne, Eine Massenintoxikation durch 2,3,6,7-Tetrachlordibenzo-Dioxin. From Int. Agency for Research on Cancer. Der Hautarzt, 24:149–152.

Goldstein, J. A. 1979. The Structure-Activity Relationships of Halogenated Biphenyls as Enzyme Inducers. Ann. New York Acad. Sci., 320:164–178.

Goldstein, J. A., et al. 1978. Effects of Pentachlorophenol on Hepatic Drug Metabolism and Porphyria Related to Contamination with Chlorinated Dibenzo-*p*-Dioxins. Environmental Protection Agency, Research Triangle Park, North Carolina.

Goldston, A. W. 1978. Herbicides: A Mixed Blessing. Bio-Science, 29(2):85–89, February.

Goodell, (Senator). 1970. Authorization of Appropriations for Military Procurement during Fiscal Year 1971-Amendment. Congressional Record-Senate, July 16, pp. 24661–24670.

Grant, W. F. 1979. The Genotoxic Effects of 2,4,5-T. Mutation Res., 65(2):83–119.

Gray, A. P., et al. 1976. Synthesis of Specific Polychlorinated Dibenzo-*p*-Dioxins. J. Org. Chem., 41(14):2435–2437.

Green, S., and F.S. Moreland. 1975. Cytogenetic Evaluation of Several Dioxins in the Rat (Abstract No. 99). Toxicol. Appl. Pharmacol., 33:161.

Green, S., F. S. Moreland, and C. Sheu. 1977. Cytogenetic Effects of 2,3,7,8-TCDD on Rat Bone Marrow Cells. FDA By Lines, 6:292–294.

Greig, J. B., and G. Osborne. 1978. Changes in Rat Hepatic Cell Membranes during 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Intoxication. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallaro, and G. Galli, eds., SP Medical and Scientific Books, NY.

Greig, J. B., D. M. Taylor, and J. D. Jones. 1974. Effects of TCDD on Stimulated DNA Synthesis in the Liver and Kidney of the Rat. Chem. Biol. Interactions, 8:31–39.

Greig, J. B., et al. 1973. Toxic Effects of 2,3,7,8-TCDD. Fd. Cosmet. Toxicol., 11:585–595.

Gribble, W. G. 1974. TCDD, a Deadly Molecule. Chemistry, 47(2):15–18, February.

Gross, M. L. 1978. Personal communication.

Guenthner, T. M., and D. W. Nebert. 1977. Cytosolic Receptor for Aryl Hydrocarbon Hydroxylase Induction by Polycyclic Aromatic Compounds. Biol. Chem., 24:8981–8989.

Guenthner, T. M., et al. 1979a. Evidence in Rat and Mouse Liver for Temporal Control of Two Forms of Cytochrome P-450 Inducible by TCDD. Environ. J. Biochem., 91(2):449–456.

Guenthner, T. M., et al. 1979b. Microsomal Aryl Hydrocarbon Hydroxylase in Rat Adrenal: Regulation by ACTH but not by Polycyclic Hydrocarbons. Mol. Pharmacol., 15:719–728.

Gupta, B. N., et al. 1973. Pathologic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Laboratory Animals. Environmental Health Perspectives, 5:125–140.

Gustafsson, J. A., and M. Ingelman-Sundberg. 1979. Changes in Steroid Hormone Metabolism in Rat Liver Microsomes Following Administration of TCDD. Biochemical Pharmacology, 28:497–499.

Gustafsson, J., et al. 1979. Mechanisms Involved in Tissue Responsiveness to Chemical Carcinogens and in Formation of Carcinogenic Metabolites from Aromatic Hydrocarbons. Toxicology Research Projects Directory, 4:9.

Hanna, R. M., and D. R. Goldberg. n.d. Dioxin Monitoring Project: Final Report, Region II c/o Rutgers University, U.S. EPA Files. Unpublished.

Hardell, L. 1979. Malignant Lymphoma of Histiocytic Type and Exposure to Phenoxyacetic Acids or Chlorophenols. Lancet, 55–56, January 6.

Hardell, L., and A. Sandstrom. 1978. Malignant Mesenchymal Soft-Tissue Tumors and Exposure to Phenoxy Acid or Chlorophenols. A Case Control Study. Lakartidringen, 75(49):3535–3536.

Hardell, L., et al. 1974. Case-Control Study of Soft-Tissue Sarcomas and Exposure to Phenoxyacetic Acids of Chlorophenols. Br. J. Cancer, 39(6):711–717.

Harless, R. L. 1976. Presentation Given at TCDD Workshop, Universita Di Milano, Institute Di Farmacologia. U.S. EPA Files. Unpublished.

Harless, R. L. 1980. Direct Testimony before the Administrator, U.S. EPA, Re: FIFRA Docket Nos. 415 et al. EPA Exhibit No. 212. April 23.

Harless, R. L. and A. Dupuy. 1979. Personal communication.

Harris, M. W., et al. 1973. General Biological Effects of TCDD in Lab Animals. Environmental Health Perspectives, 5:101–109, September.

Harrison, D. D., C. I. Miller, and R. C. Crews. 1979. Residual Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) near Herbicide Storage and Loading Areas at Eglin Air Force Base, Florida. AFATL-TR-79-20. February.

Hass, J. R., et al. 1978. Anal. Chem., 50:1474.

Harrison, W. S., A. T. Peters, and F. M. Rowe. 1943. Polyhalogeno-*o*-Anisidines and Their Derivatives. J. Am. Chem. Soc., pp. 235–237.

Haskelberg, L. 1947. The Halogenation of Aryloxyacetic Acids and Their Homologs. J. Org. Chem., 12:426–433.

Hatfield, M. O., (Senator). 1977. Written communication to D. Costle, U.S. EPA Administrator, November 3.

Hawley, G. 1971. Condensed Chemical Dictionary. 8th ed., Van Nostrand-Reinhold Co., New York.

Hawley, G., 1977. Condensed Chemical Dictionary. 9th ed., Van Nostrand-Reinhold Co., New York.

Hay, A. 1976a. Toxic Cloud over Seveso. Nature, 262:636–638, August 19.

Hay, A. 1976b. Seveso: The Problems Deepen. Nature, 264:309–310, November 18.

Hay, A. 1977a. Seveso Solitude. Nature, 267:384–385, June 2.

Hay, A. 1977b. Identifying Carcinogens. Nature, 269:468–470, October 6.

Hay, A. 1978a. Vietnam's Dioxin Problem. Nature, 271:597–598, February 16.

Hay, A. 1978b. Company's Claim Sparks Fresh Controversy over Seveso. Nature, 247:108, July.

Helling, C. S., et al. 1973. Chlorodioxins in Pesticides, Soils, and Plants. J. Environ. Quality, 2(2): 171–178.

Hepner, G. W. 1979. Detection of Carcinogen-Induced Stimulation of Cytochrome P-448-Associated Enzymes by $^{14}CO_2$ Breath Analysis Studies Using Dimethylaminoazobenzene. Gastroenterology, 76(2):267–271.

Higgenbotham, G. R., et al. 1968. Chemical and Toxicological Evaluations of Isolated and Synthetic Chloro. Derivatives of Dibenzo-*p*-Dioxin. Nature, 220:702–703.

Highman, B., T. B. Gaines, and J. J. Schumacher. Renal Alkaline Phosphatase Activity in Fetal Offspring of Maternal Mice Given 2,4,5-Trichlorophenoxyacetic Acid. University of Arkansas College of Medicine, Little Rock, Arkansas; and the National Center for Toxicological Research, Jefferson, Arkansas.

Highman, B., et al. 1977. Retarded Development of Fetal Renal Alkaline Phosphatase in Mice Given 2,4,5-T. J. Toxicol. Environ. Health, 2:1007–1018.

Homberger, E., et al. 1979. The Seveso Accident: Its Nature, Extent and Consequence. Givauden Research Company, Ltd. and F. Hoffman-LaRoche and Co., Ltd. Confidential.

Hook, G. E. R., J. K. Haseman, and G. W. Lucier. 1975. Induction and Supression of Hepatic and Extrahepatic Microsomal Foreign-Compound-Metabolizing Enzyme Systems by 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Chem. Biol. Interactions, 10:199–214.

Hook, G. E. R., et al. 1975. 2,3,7,8-TCDD Induced Changes in the Hydroxylation of Biphenyl by Rat Liver Microsomes. Biochemical Pharmacology, 24:335–340.

Hook, J. B., et al. 1978. Renal Effects of 2,3,7,8-TCDD. Environ. Sci. Res., 12:381–388.

Howard, K. J. Written communication to D. R. Watkins, U.S. EPA, IERL-Ci., September 30, 1980.

Huckins, J. N., D. L. Stalling, and W. A. Smith. 1978. Journal of the AOAC, 61:32.

Huetter, R. 1980. Written communication to D. R. Watkins, U.S. EPA, IERL-Ci. January 9.

Huff, J. E., and J. S. Wassom. 1974. Health Hazards from Chemical Impurities; Chlorinated Dibenzodioxins and Chlorinated Dibenzofurans. Intern. J. Environ. Studies, 6:13–17.

Hughes, B. M., et al. 1975. Analytical Methodology for Herbicide Orange Volume I. Determination of Chemical Composition. Aerospace Research Laboratories Technical Report TR75-0110. Volume I.

Hugounenq, L. 1890. Derives Chlores l'anisol et du phenol ordinaire. Ann. Chim. Phys., 20:546.

Hummel, R. A. 1977. Cleanup Techniques for the Determination of Parts per Trillion Residue Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD). J. Agric. Food Chem., 25(5):1049-1053.

Hunt, D. F., T. M. Harvey, and J. W. Russel. 1975. J.C.S. Chem. Comm., Vol. 151.

Hunter, W. H., and L. M. Seyfried. 1921. A Catalytic Decomposition of Certain Phenol Silver Salts. V. The Action of Iodine on the Sodium Salt of Trichlorophenol. J. Am. Chem. Soc., 43:151–159.

Hussain, S. L., et al. 1972. Mutagenic Effects of TCDD on Bacterial Systems. Ambio., 1:32–33.

In Brief. 1977. A Review of Water and Pollution Control News. Italian Poison Zone Will Close Factories. July.

Ingersoll, B. 1979. Creek Closed by Superpoison. Chicago Sun-Times. June 2.

Innes, J. R. M. 1969. Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note. J. National Cancer Institute, 42(6):1101-1114.

Inubushi, Y., et al. 1958. Dibenzo-*p*-Dioxin Derivatives. XXIV. Friedel-Crafts Reaction of Dibenzo-*p*-Dioxin Derivatives. Yakugaku Zasshi, 78:581. Chemical Abstracts, 52:18421, 1958.

Isensee, A. R. 1978. Bioaccumulation of 2,3,7,8-TCDD. Ecol. Bull., 27:255-262.

Isensee, A. R., and G. E. Jones. 1971. Absorption and Translocation of Root and Foliage Applied 2,4-Dichlorophenol, 2,7-Dichlorodibenzo-*p*-Dioxin, and 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. J. Agric. Food Chem., 19(6):1210-1214.

Isensee, A.R., and G.E. Jones. 1975. Distribution of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in Aquatic Model Ecosystem. Environmental Science and Technology, 9(7):668-672.

Jackson, W. T. 1972. Regulation of Mitosis 3 Cytological Effects of 2,4,5-Trichlorophenoxyacetic Acid and of Dioxin Contaminants in 2,4,5-T Formulations. J. Cell Sci., 10:15-25.

J. Am. Chem. Soc. 1960. Phenethicillin, 82:3934.

Jansson, B., G. Sundstrom, and B. Ahling. 1978. Formation of Polychlorinated Dibenzo-*p*-Dioxins during Combustion of Chlorophenol Formulations. Sci. Total Environ., 10(3):209-218.

Jensen, S., and L. Renberg. 1972. Contaminants in Pentachlorophenol: Chlorinated Dioxins and Predioxins. Ambio., 1(2):62-65.

Jensen, S., and L. Renberg. 1973. Chlorinated Dimers Present in Several Technical Chlorophenols Used as Fungicides. Environmental Health Perspectives, 5:37-41, September.

Jirasek, L., J. Kalensky, and K. Kubec. 1973. Acne Chlorina, Porphyria Cutanea Tarda, and Other Manifestations of General Intoxication During the Manufacture of Herbicides. II. Ceskoslovenska Dermatologies, 48(5):306-317.

Jirasek, L., et al. 1974. Acne Chlorina, Porphyria Cutanea Tarda, and Other Manifestations of General Intoxication During the Manufacture of Herbicides. II. Ceskoslovenska Dermatologies, 49(3):145-147.

Jirasek, L., et al. 1976. Chloracne, Prophyria Cutanea Tarda, and Other Poisonings Due to the Herbicides. Hautarzt, 27(7):328-333.

Johnson, J. E. 1971. Safety in the Development of Herbicides. Down to Earth, 27(1):1-7.

Johnson, R. L. 1973. Chlorinated Dibenzodioxins and Pentachlorophenol. Environmental Health Perspectives, 5:171-175, September.

Jones, G. 1975. A Histochemical Study of the Liver Lesion Induced by 2,3,7,8-TCDD (Dioxin) in Rats. J. Path., 116:101-105.

Jones, K. G., and G. D. Sweeney. 1977. Pathogenesis of Porphyria Cutanea Tarda. Gastroenterology, 73(5):A-29.

Jones, R. A. 1970. An Introduction to Gas-Liquid Chromatography. Academic Press, New York.

Julia, M., and M. Baillarge. 1953. Substituted *p*-Phenoxyphenylacetic Acids. Bull. Soc. Chim. France, 644, Chemical Abstracts, 48:5831, 1954.

Junk, G. A., et al. 1976. J. Am. Water Works Assoc., 68-218.

Kapetanovic, I.M. 1979. Metabolic Structure-Activity Relationships for a Homologous Series of Phenacetic Analogs. J. Pharmacol. Exp. Ther., 209:20–24.

Kaupp, J., and H. Klug. 1962. Perchlorodiphenylene Dioxide. German Patent No. 1,092,480 to Farbwerke Hoechst A. G. See Chemical Abstracts, 56:14302.

Kearney, P. C., E. A. Woolson, and C.P. Ellington, Jr. 1972. Persistence and Metabolism of Chlorodioxins in Soils. Environmental Science and Technology, 6(12):1017–1019, November.

Kearney, P.C., et al. 1973a. Environmental Significance of Chlorodioxins. In: Chlorodioxins—Origin and Fate, E.H. Blair, ed. American Chemical Society, Washington, DC, pp. 105–111.

Kearney, P.C., et al. 1973b. TCDD in the Environment: Sources, Fate, and Decontamination. Environmental Health Perspectives, 5:275–277, September.

Keimatsu, I., and E. Yamaguchi. 1936. Diphenyl Ether Derivatives. J. Pharm. Soc. Japan, 56:680.

Kende, A.S., and J.J. Wade. 1973. Synthesis of New Steric and Electronic Analogs of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Environmental Health Perspectives, 5:49–59. September.

Kende, A. S., et al. 1974. Synthesis and Fourier Transform Carbon-13 Nuclear Magnetic Resonance Spectroscopy of New Toxic Polyhalodibenzo-*p*-Dioxins. J. Org. Chem., 39:931.

Kennedy, M. V., B. J. Stojanovic, and F. L. Shuman, Jr. 1969. Chemical and Thermal Methods for Disposal of Pesticides. Residue Reviews, 29:89.

Khera, K.S., and W.P. McKinley. 1972. Pre- and Postnatal Studies on 2,4,5-Trichlorophenoxyacetic Acid, 2,4-Dichlorphenoxyacetic Acid and Their Derivatives in Rats. Toxicol. Appl. Pharmacol., 22:14–28.

Khera, K.S., and J.A. Ruddick. 1973. Polychlorodibenzo-*p*-Dioxins Perinatal Effects and the Dominant Lethal Test in Wistar Rats. In: Chlorodioxins—Origin and Fate, E.H. Blair, ed. American Chemical Society, Washington, DC, pp. 70–84.

Kimble, B.J., and M.L. Gross. 1980. Tetrachlorodibenzo-*p*-Dioxin Quantitation in Stack-Collected Coal Fly Ash. Science, 207:59–61, January 4.

Kimbrough, R.D. 1971. Review of the Toxicity of Hexachlorophene. Arch. Environ. Health, 23:119–122.

Kimbrough, R.D. 1972. Toxicity of Chlorinated Hydrocarbons and Related Compounds. Arch. Environ. Health, 25:125–131.

Kimbrough, R.D. 1974. The Toxicity of Polychlorinated Polycyclic Compounds and Related Chemicals. CRC Critical Reviews in Toxicology, 2(4):445–498.

Kimbrough, R.D. 1976. Hexachlorophene: Toxicity and Use as an Antibacterial Agent. Essays in Toxicology, 7:99–120.

Kimbrough, R.D., et al. 1977. Epidemiology and Pathology of a Tetrachlorodibenzodioxin Poisoning Episode. Arch. Environ. Health, 32(2):77–86.

Kimmig, J., and K.H. Schulz. 1957. Occupational Acne (Chloracne) Caused by Chlorinated Aromatic Cyclic Ethers. Dermatologica, 115:540–546.

Kirsch, R. et al. 1975. Structural and Functional Studies of Ligandin, a Major Renal Organic Anion-Binding Protein. J. Clin. Invest. 55:1009–1019.

Kiser, R.W. 1965. Introduction to Mass Spectrometry and Its Applications. Prentice-Hall, Englewood Cliffs, NJ.

Kitchin, K.T., and J.S. Woods. 1978. 2,3,7,8-TCDD Induction of Aryl Hydrocarbon Hydroxylase in Female Rat Liver. Evidence for De Novo Synthesis of Cytochrome P-448. Mol. Pharmacol., 19:890–899.

Kitchin, K.T., et al. 1979. TCDD Effects on Hepatic Microsomal Cytochrome P-448-Mediated. Toxicol. Appl. Pharmacol., 47(3):537–546.

Klecka, G.M., and D.T. Gibson. 1979. Metabolism of Dibenzo[1,4]dioxin by a *Pseudomonas* Species. Biochem. J., 180:639–645.

Kluwe, W.M. 1978. Selective Modification of the Renal and Hepatic Toxicities of Chloroform by Induction of Drug-Metabolizing Enzyme Systems in Kidney and Liver. J. Pharmacol. Exp. Ther., 207(2):449–473.

Kocher, C.W., et al. 1978. A Search for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Beef Fat. Bulletin of Environmental Contamination and Toxicology, 19:229–236.

Kociba, R.J. 1979. Toxicology Studies of TCDD in Rats. Dev. Toxicol. Environ. Sci., 281:7.

Kociba, R.J., et al. 1976. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)—Results of a 13-Week Oral Toxicity Study in Rats. Toxicol. Appl. Pharmacol., 35:553–574.

Kociba, R.J., et al. 1978. Results of a Two-Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Rats. Toxicol. Appl. Pharmacol., 46(2):279–304.

Kouri, R.E., et al. 1978. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin as Cocarcinogen Causing 3-Methylcholanthrene-Initiated Subcutaneous Tumors in Mice Genetically "Nonresponsive" at Ah Locus. Cancer Research, 38:2777–2783, September.

Kozak, V.P., et al. 1979. Reviews of the Environmental Effects of Pollutants: XI. Chlorophenols. ORNL/EIS-128, EPA-600/1-79-012, pp. 464–465.

Kulka, M. 1961. Octahalogenodibenzo-*p*-Dioxins. Can. J. Chem., 39.

Kulka, M. 1965. Perhalodibenzo-*p*-Dioxins. Canadian Patent No. 702,144 to Dominion Rubber Co., Ltd. See Chem. Abstracts, 62:16261.

Kupfer, D. 1975. Effects of Pesticides and Related Compounds on Steroid Metabolism and Function. CRC Critical Reviews in Toxicology, 4(1):83–124, October.

Lancet. 1976. Seveso. 2(7980):297, August 7.

Lancet. 1977. Long-Term Effects of Dioxin Exposure. 1:8014, April 2.

Langer, H.G., T.P. Brady, and P.R. Briggs. 1973. Formation of Dibenzo-Dioxins and Other Condensation Products from Chlorinated Phenols, and Derivatives. Environmental Health Perspectives, 5:3–9, September.

Langer, H.G., et al. 1973. Thermal Chemistry of Chlorinated Phenols. In: Chlorodioxins—Origin and Fate, E. Blair, ed. American Chemical Society, Washington, DC, pp. 26–32.

Laporte, J.R. 1977. Effects of Dioxin Exposure. Lancet, II 8028:82–83, July 9.

Lawless, E.W., T.L. Ferguson, and A.F. Meiners. 1975. Guidelines for the Disposal of Small Quantities of Unused Pesticides. EPA-670/2-75-057.

Lawrence Eagle Tribune. 1978. Tot, 3, May Be Vietnam War Casualty. October 30, pp. A-1, A-16.

Lee, D., et al., eds. 1973. Environmental Health Perspectives, Experimental Issue No. 5, September.

Leng, M.L. 1976. Comparative Metabolism of Phenoxy Herbicides in Animals. In: Fate of Pesticides in Large Animals, G.W. Ivie and H.W. Dorough, eds. Academic Press, New York. pp. 53–76.

Leng, M.L. 1977. Are Lawn Weed Killers Really Hazardous? Dow Chemical U.S.A. Report, August 29.

Lester, R. G., and J. F. Brennan. 1972. Catalytic Preparation of Dibenzo-Dioxins. U.S. Patent No. 3,679,704. Chemical Abstracts, 77:114413g.

Liberti, A. 1978. Field Photodegradation of TCDD by Ultraviolet Radiations. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallaro, and G. Galli, eds., SP Medical and Scientific Books, New York, London.

Lira, P., M.D. 1978. Velsicol Corp., Personal communication, August 29.

Littlewood, A.B. 1970. Gas Chromatography. 2d ed., Academic Press, New York.

Lucier, G. W. 1979. Developmental Toxicology of the Halogenated Aromatics: Effects on Enzyme Development. Ann. New York Acad. Sci., 320:449–457.

Lucier, G.W., O.S. McDaniel, and G.E.R. Hook. 1975. Nature of the Enhancement of Hepatic Uridine Diphosphate Glucuronyl-Transferase Activity by 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Rats. Biochem. Pharmacol. 24:325–334.

Lucier, G. W., et al. 1973. TCDD-Induced Changes in Rat Liver Microsomal Enzymes. Environmental Health Perspectives, 5:199–209, September.

Lucier, G. W., et al. 1979. Laboratory Studies on the Immune Effects of Halogenated Aromatics. Ann. New York Acad. Sci., 320:473–486.

Luster, M.I. 1979a. Effects of Brief In Vitro Exposure to TCDD on Mouse Lymphocytes. J. Environ. Pathol. Toxicol., 2(4):965–977.

Luster, M. I. 1979b. Immunochemistry of Dioxin Action on the Lymphocyte. Tox. Research Proj. Directory, 04:06.

Luster, M. I., et al. 1978. Inability of Passive Antibodies to Reverse the Effects of Dioxin Toxicity. Chemosphere, 7(1):29–34.

Madge, D.S. 1977. Effects of Trichlorophenoxyacetic Acid and Chlorodioxins on Small Intestinal Function. Gen. Pharmacol., 8(5–6):319–329.

Madhukar, B. V., et al. 1979a. Comparison of Induction Patterns of Rat Microsomal Mixed-Function Oxidases by Pesticides and Related Chemicals. Pestic. Biochem. Physiol., 11:301–308.

Madhukar, B. V., et al. 1979b. Depression of ATPase Activity in Hepatocyte Surface Membranes of Rats by 2,3,7,8-TCDD Treatment. Toxicol. Appl. Pharmacol., 48(1):A152.

Manis, J. 1977. Induction of Intestinal from Transport by 2,3,7,8-TCDD, an Environmental Pollutant and Potent Inducer of Aryl Hydrocarbon Hydroxylase. Clin. Res., 25(3):468A.

Manis, J. 1979. Intestinal Organic Anion Transport, Glutathione Transferase and Aryl Hydrocarbon Hydroxylase Activity: Effect of Dioxin. Life Sci., 24:1373–1380.

Manis, J., and G. Kim. 1979. Stimulation of Iron Absorption by Polychlorinated Aromatic Hydrocarbons. Am. J. Physiol., 236: E763–E768.

Manske, R. H. F. 1949. 2,4-Dichlorophenoxyacetic Acid. U.S. Patent No. 2,471,575. Assigned to United States Rubber Company, May 31.

March, J. 1968. Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. McGraw-Hill Book Co., NY, pp. 519–520.

Marselos, M. 1979. Comparison of Phenobarbital and Carcinogen-Induced Aldehyde Dehydrogenases in the Rat. Biochem. Biophys. ACTA, 583(1):110.

Marselos, M., et al. 1978. Responses of the D-Gluccionic Acid Pathway in Rat Tissues to Treatment with TCDD. Xenobiotica, 8(7):397–402.

Matsumura, F., and H. J. Benezet. 1973. Studies on the Bioaccumulation and Microbial Degredation of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Environmental Health Perspectives, 5:253–258, September.

Mauk, C. E., H. W. Prengle, Jr., and J. E. Payne. 1976. Oxidation of Pesticides by Ozone and Ultraviolet Light, U.S. Army Mobility Equipment Research and Development Command, AD-A028 306/9ST.

May, G. 1973. Chloracne from the Accidental Production of Tetrachlorodibenzodioxin. British J. Industrial Medicine, 30:276–283.

McCann, J., et al. 1976. Detection of Carcinogens as Mutagens in the *Salmonella*/Microsome Test: Assay of 300 Chemicals. Proc. Nat. Acad. Sci. 73:950–954.

McConnell, E.E., and J.A. Moore. 1976. The Comparative Toxicity of Chlorinated Dibenzo-*p*-Dioxin Isomers in Mice and Guinea Pigs. Toxicol. Appl. Pharmacol., 37:146.

McConnell, E. E., J. A. Moore, and D. W. Dalgard. 1978. Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Rhesus Monkeys *(Macaca Mulatta)* Following a Single Oral Dose. Toxicol. Appl. Pharmacol., 43:175–187.

McConnell, E. E., et al. 1978. The Comparative Toxicity of Chlorinated Dibenzo-*p*-Dioxins in Mice and Guinea Pigs. Toxicol. Appl. Pharmacol., 44:335–356.

McFadden, W. 1973. Techniques of Combined Gas Chromatography/Mass Spectrometry. Wiley-Interscience, NY.

McInty, L. 1976. The Graveyard on Milan's Doorstep. New Science, 71(104): 383–385.

McIntyre, T. J. (Senator). 1970. Herbicide Program in Vietnam. Congressional Record, August 25, pp. 29932–30012.

McLafferty, F. W., ed. 1963. Mass Spectrometry of Organic Ions. Academic Press, NY.

McNulty, W. P., M.D. 1978a. Written communication to U.S. EPA Office of Pesticide Programs, July 27.

McNulty, W. P., M.D., 1978b. Oregon Regional Primate Research Center, personal communication, August 8.

McNulty, W. P., et al. 1979a. PCB and TCDD Orofacial Teratogenesis in *Macaca Mulatta*. Toxicology Research Projects Directory, 04:101.

McNulty, W. P., et al. 1979b. Toxicity of TCDD for Rhesus Monkeys: Brief Report. Pub. No. 878, Oregon Primate Research Center.

McQueen, E. G., et al. 1977. 2,4,5-T and Human Birth Defects, New Zealand Department of Health, June.

Mercier, M.J. 1976. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin: An Overview. In: Proceedings of the Expert Meeting on the Problems Raised by TCDD Pollution, A. Berlin, A. Buratta, and M.T. Van der Venne, eds. Milan. In press.

Merck Index. 1978. 9th ed., M. Windholz, ed. Merck & Co., Inc., Rahway, NJ.

Merenda, J. J. 1979. TSCA Section 8(e) submission on Polychlorinated Dibenzo-*p*-Dioxins (PCDD's). Letters and enclosures to E.Blair, vice president Dow

Chemical Company, from Director, Assessment Division, EPA. EPA Document Control No. 8EHQ-1178-0209, February 15.

Merritt, W. H., Jr., and J. Dean. 1974. Instrumental Methods of Analysis. 5th ed. Van Nostrand, NY.

Merz, V., and W. Weith. 1872. Zur Kenntnis des Perchlorophenols. Ber., 5:460.

Meselson, M., P.W. O'Keefe, and R. Baughman. 1978. The Evaluation of Possible Health Hazards from TCDD in the Environment. Presentation for Symposium on the Use of Herbicides in Forestry. Arlington, Virginia, February 21–22.

Miller, R. A., L. A. Norris, and C. L. Hawkes. 1973. Toxicity of 2,3,7,8-TCDD in Aquatic Organisms. Environmental Health Perspectives, 5:177–187, September.

Miller, S. 1979. Source of Dioxins. Chemical and Engineering News. March 12, p. 4.

Milnes, M. H. 1971. Formation of 2,3,7,8-Tetrachlorodibenzodioxin by Thermal Decomposition of Sodium 2,4,5-Trichlorophenate. Nature (London), 232:395–396, August 6.

Mitchell, L. C. 1961. The Effect of Ultraviolet Light on 141 Pesticide Chemicals. J. Assoc. Offic. Agr. Chem., 44:643–712.

MITRE Corporation. 1977. The Analysis of Existing Wood Preserving Techniques and Possible Alternatives. Technical Report 7520. Prepared for U.S. EPA, Contract No. 68-01-4310.

Modell, J., R.P. deFilippi, and V. Krukonis. 1978. Regeneration of Activated Carbon with Supercritical Carbon Dioxide. Presented at the ACS Conference, Miami, Florida. September 14.

Monsanto Research Corp. and Research Triangle Institute. 1976. Chapter 6: The Industrial Organic Chemicals Industry—Part I. In: Industrial Process Profiles for Environmental Use. EPA-68-02-1302 and 1325, Research Triangle Park, North Carolina.

Moore, J. A. 1979. A Pesticide. Science, 203(4382):741–742. February 23.

Moore, J. A., and R. E. Faith. 1976. Immunologic Response and Factors Affecting Its Assessment. Environmental Health Perspectives, 18:125–132.

Moore, J. A., B. N. Gupta, and J. G. Vos. 1976. Toxicity of 2,3,7,8-Tetrachlorodibenzofuran—Preliminary Results. In: National Conference on Polychlorinated Biphenyls, Chicago, 1975. EPA-560/6-75-004.

Moore, J.A., M.W. Harris, and P.W. Albro. 1978. Tissue Distribution of (^{14}C) Tetrachlorodibenzo-*p*-Dioxin in Pregnant and Neonatal Rats. National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Moore, J. A., et al. 1973. Postnatal Effects of Maternal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD). Environmental Health Perspectives, 5:81–85.

Moye, A. L. 1972. Experiencing Relevancy in Organic Chemistry. Hexachlorophene: The Great Clean-All. Journal of Chemical Education, 49(11): 770–771, November.

Murray, F. J., et al. 1978. Three-Generation Reproduction Study of Rats Ingesting TCDD. Toxicol. Appl. Pharmacol., 41:200–201.

Nagayama, J., M. Kuratsune, and Y. Masuda. 1976. Determination of Chlorinated Dibenzofurans in Kanechlors and "Vusho Oil." Bulletin of Environmental Contamination and Toxicology, 15:9–13.

Nash, R. G., and M. L. Beall, Jr. 1977. Environmental Distribution of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) Applied with Silvex to Turf in Microagroecosystem. Final Report. U.S. EPA-USDA Interagency Agreement, EPA-IAG-D6-0054, ARS 173, EPA No. 1001-704.

Nash, R. G., and M. L. Beall, Jr. 1978. A Microagroecosystem to Monitor the Environmental Fate of Pesticides. Pesticide Degradation Laboratory, ARS, USDA, Beltsville, MD. Unpublished.

National Academy of Sciences. 1974. Committee on the Effects of Herbicides in South Vietnam, Part A. Summary and Conclusions. Washington, DC.

National Academy of Sciences. 1977. Drinking Water and Health. Part II, Chapter VI and Bibliography.

Nature. 1970. Another Herbicide on the Blacklist. 226:309–311.

Neal, R. A. 1979. Mechanisms of Toxicity of the Chlorinated *p*-Dioxins. Toxicology Research Projects Directory, 04:11.

Nebert, D. W., S. S. Thorgeirsson, and J. S. Felton. 1976. Genetic Differences in Mutagenesis, Carcinogenesis, and Drug Toxicity. In: In Vitro Metabolic Activation in Mutagenesis Testing, F. J. deSerrers, et al., ed. Elsevier/North Holland Publishing Co., Amsterdam, 105-124.

Nelson, C. J., et al. 1979. Retrospective Study of the Relationship Between Agricultural Use of 2,4,5-T and Cleft Palate Occurrence in Arkansas. Teratology, 19:377–384.

Nelson, G. (Senator). 1973. Statement on Dioxins. Congressional Record, January 17.

Nelson, J. D., et al. 1977. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin In Vitro Binding to Rat Liver Microsomes. Bulletin of Environmental Contaminants and Toxicology, 18(1):9–13.

Nestrick, T., L. Lamparski, and R. Stehl. 1979. Synthesis and Identification of the 22 Tetrachlorodibenzo-*p*-Dioxin Isomers by High Performance Liquid Chromatography and Gas Chromatography. Anal. Chem., 51(13):2273–2281.

Neubert, D., and I. Dillmann. 1972. Embryotoxic Effects in Mice Treated with 2,4,5-Trichlorophenoxyacetic Acid and 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Naunyn-Schmiedeberg's Arch. Exp. Path. Pharmacol, 272:243–264.

Neubert, D., et al. 1973. A Survey of the Embryotoxic Effects of TCDD in Mammalian Species. Environmental Health Perspectives, 5:67–79.

Newton, M., and S. Snyder. 1978. Exposure of Forest Herbivores to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in Areas Sprayed with 2,4,5-T. Bulletin of Environmental Contamination and Toxicology, 20(6):743–750.

Nicholson, W. and J. Moore, eds. Health Effects of Halogenated Aromatic Hydrocarbons. Annals of the New York Academy of Science. 1979. Vol. 320.

Nilsson, C. A., et al. 1974. Chromatographic Evidence for the Formation of Chlorodioxins from Chloro-2-Phenoxyphenols. J. Chromatography, 96:137–147.

Niwa, A., et al. 1975. Genetic Expression of Aryl Hydrocarbon hydroxylase Activity in the Mouse. Archives of Biochemistry and Biophysics, 166:559–564.

Nolan, R. J., et al. 1979. Elimination of Tissue Distribution of TCDD in Female Guinea Pigs Following a Single Oral Dose. Toxicol. Appl. Pharmacol., 48(1):A162.

Norback, D. H. 1975. Tissue Distribution and Excretion of Octachlorodibenzo-*p*-Dioxin in the Rat. Toxicol. Appl. Pharmacol., 32:330–338.

Norback, D. H., and J. R. Allen. 1973. Biological Responses of the Nonhuman Primate, Chicken and Rat to Chlorinated Dibenzo-*p*-Dioxin Ingestion. Environmental Health Perspectives, 5:233–240.

Norman, R. L. 1978. Identification of the Major Cytochrome P-450 Form Transplacentally Induced in Neonatal Rabbits by 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. J. Biol. Chem., 253(23):8640–8647.

Oberacker, D. A., and S. Lees. 1977. Microwave Plasma Detoxification of Hazardous and Toxic Materials. In: News of Environmental Research in Cincinnati. U.S. EPA, Municipal Environmental Research Laboratory.

Occupational Safety and Health Reporter. 1979. Health Hazards: NIOSH Begins Epidemiological Study of All Workers Exposed to Dioxin TCDD. Vol. 9, No. 26, November 29.

Offut, C. 1978. EPA Office of Toxic Substances, personal communication, September 8.

Oishi, S., M. Morita, and H. Fukuda. 1978. Comparative Toxicity of Polychlorinated Biphenyls and Dibenzofurans in Rats. Toxicol. Appl. Pharmacol., 43:13–22.

O'Keefe, P. W., M. S. Meselson, and R. W. Baughman. 1978. Neutral Clean-Up Procedures for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Residues in Bovine Fat and Milk. Journal of the AOAC, 61:621–626.

Olie, L., P. L. Vermeulen, and O. Hutzinger. 1977. Chlorodibenzo-*p*-Dioxins and Chlorodibenzofurans Are Trace Components of Fly Ash and Flue Gas of Some Municipal Incinerators in the Netherlands. Chemosphere, 8:455–459.

Oliver, R. J. 1975. Toxic Effects of 2,3,7,8-Tetrachlorodibenzo 1,4 Dioxin in Laboratory Workers. British J. of Industrial Medicine, 32:49–53.

Ott, P., M.D. 1978. EPA, personal communication, August 29.

Ottinger, R. S., et al. 1973. Recommended Methods of Reduction, Neutralization, Recovery, or Disposal of Hazardous Waste. Volume 3. NTIS PB-224 582.

Parkki, M.G., and A.Aitio. 1978. Induction of Drug Metabolizing Enzymes in Different Rat Tissues by TCDD. Arch. Toxicol. ISS Supl. 1, 261–265.

Parks, M. 1978. The Seveso Case. EPA Journal, 4(8)11–15, 35, September.

Parsons, T., ed. 1977. Chapter 8: Pesticides Industry. In: Industrial Process Profiles for Environmental Use. Radian Corp. EPA-68-02-1319, Research Triangle Park, North Carolina.

Peracchio, A. 1979. Dow Chemical Faces Suits from Veterans of Vietnam over Babies with Defects. Newsday, copyright.

Peterson, J. 1978. Seveso: The Event. Ambio, 7(5–6):232–233.

Physicians' Desk Reference. 1978. 32d edition. Medical Economics Company, Oradell, NJ.

Piper, W. N. 1979. Toxicant Deregulation of Endocrine Heme Biosynthesis. Toxicology Research Projects Directory, 04:06.

Piper, W. N., J. Q. Rose, and P. J. Gehring. 1973. Excretion and Tissue Distribution of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in the Rat. Environmental Health Perspectives, 5:241–244.

Plimmer, J. R. 1972. Principles of Photodecomposition of Pesticides: Degradation of Synthetic Organic Molecules in the Biosphere. National Academy of Sciences, Washington, D.C.

Plimmer, J.R. 1973. Technical Pentachlorophenol: Origin and Analysis of Base-Insoluble Contaminants. Environmental Health Perspectives, 5:41–47.

Plimmer, J. R. 1978a. Approaches to Decontamination or Disposal of Pesticides: Photodecomposition. In: Disposal and Decontamination of Pesticides, M. V. Kennedy, ed. ACS Symposium Series 73, American Chemical Society, Washington, DC, pp. 12–23.

Plimmer, J. R. 1978b. Photolysis of TCDD and Trifluralin on Silica and Soil. Bulletin of Environmental Contamination and Toxicology, 20:87–92.

Plimmer, J. R., et al. 1973. Photochemistry of Dibenzo-*p*-Dioxins. In: Chlorodioxins—Origin and Fate, E. Blair, ed. American Chemical Society, Washington, DC, pp. 44–54.

Pocchiari, F. 1978. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Decontamination. In: Chlorinated Phenoxy Acids and Their Dioxins, C. Ramel, ed. Ecol. Bull. (Stockholm), 27:67–70.

Pocchiari, F., V. Silano, and A. Zampieri. 1979. Human Health Effects from Accidental Release of TCDD at Seveso, Italy. Ann. New York Acad. Sci., 311:20.

Pohland, A. E., and G. C. Yang. 1972. Preparation and Characterization of Chlorinated Dibenzo-*p*-Dioxin. J. Agric. Food Chem., 20:1093–1099.

Pohland, A. E., G. C. Yang, and N. Brown. 1973. Analytical and Confirmative Techniques for Dibenzo-*p*-Dioxins Based upon Their Cation Radicals. Environmental Health Perspectives, 5:9–13.

Pokorny, R. 1941. Some Chlorophenoxyacetic Acids. J. Am. Chem. Soc., 63:1768.

Poland, A. 1973. Chlorinated Dibenzo-*p*-Dioxins: Potent Inducer of σ-Aminolevulinic Acid Synthetase and Aryl Hydrocarbon Hydroxylase II. A Study of the Structure-Activity Relationship. Mol. Pharmacol., 9:736–747.

Poland, A., and E. Glover. 1974. Comparison of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin, a Potent Inducer of Aryl Hydrocarbon Hydroxylase, with 3-Methyl Chloranthrene. Mol. Pharmacol., 10:349–359.

Poland, A., and A. Kende. 1976. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin: Environmental Contaminant and Molecular Probe. Federal Proceedings, 35(12): 2404–2411.

Poland, A., et al. 1971. A Health Survey of Workers in a 2,4-D and 2,4,5-T Plant with Special Attention to Chloracne, Porphyria Cutanea Tarda, and Psychologic Parameters. Arch. Environ. Health, 22:316–327.

Poland, A., et al. 1976. 3,4,3,,4,-Tetrachloro Azoxybenzene and Axobenzene: Potent Inducers of Arylhydrocarbon Hydroxylase. Science, 194:627.

Poole, C. 1979. U.S. EPA, personal communication.

Purkyne, J. E., et al. 1974. Acne Chlorina, Porphyria Cutanea Tarda, A Jine Projevy Celkoue Intoxikace Pki Uyrobe Herbicid. Ceskoslovenska Dermatologie, 3(49):145–157.

Ramsey, J. C. 1979. The In Vivo Biotransformation of TCDD in the Rat. Toxicol. Appl. Pharmacol., 48(1):A162.

Rappe, C. 1978. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) Introduction. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallaro, and G. Galli, eds. SP Medical and Scientific Books, NY, pp. 9–11.

Rappe, C. 1979. Polychlorinated Dibenzodioxins and Dibenzofuran Compounds of Current Interest. Lakartidrigen, 76(1–2):21–29.

Rappe, C., et al. 1978. Formation of Polychlorinated Dibenzo-*p*-Dioxins (PCDDs) and Dibenzofurans (PCDFs) by Burning or Heating Chlorophenates. Chemosphere, 7(3):269–281.

Rawls, R. L. 1979. Dow Finds Support, Doubt for Dioxin Ideas. Chemical and Engineering News, 57(7):23–29, February 12.

Reece, M. 1978a. EPA, personal communication. September 18.

Reece, M. 1978b. Written communication from U.S. EPA Pesticide Programs. October 10.

Reece, M. 1978c. EPA, personal communication. November 2.

Reggiani, G. 1977. Medical Problems Raised by the TCDD Contamination in Seveso, Italy. Presented at the 5th Interntional Conference on Occupational Health in the Chemical Industry (Medichem), San Francisco, September 5–10.

Reggiani, G. 1978. Medical Problems Raised by the TCDD Contamination in Seveso, Italy. Arch. Toxicol., 40(3):161–188.

Reggiani, G. 1979a. Estimation of the TCDD Toxic Potential in the Light of the Seveso Accident. Arch. Toxicol. (Suppl.), 291–302.

Reggiani, G. 1979b. TCDD Contamination in Italy: The Risk Assessment of Low-Level Exposure, Cumulative Effect and Long-Term Consequences. Toxicol. Appl. Pharmacol., 48(1):A180.

Revzin, P. 1979. Chemical Cloud Still Casts Long Shadow over Seveso, Italy. The Wall Street Journal, July 10.

Richards, B. 1979a. Pesticide Waste Dumping Probed near Little Rock. The Washington Post. May 19.

Richards, B. 1979b. Arkansas Pesticide Plant Being Investigated. The Washington Post. June 17.

Richards, B. 1979c. Arkansas Site May Hold Clue. The Washington Post. July 25.

Riley, B. T. 1975. Summation of Conditions and Investigations for the Complete Combustion of Organic Pesticides. U.S. Environmental Research Laboratory, EPA-600/2-75-044.

Robbins, A. 1979. Dioxin Studies. Science 205:1332, September 28.

Roboz, J. 1968. Introduction to Mass Spectrometry. Wiley-Interscience, NY.

Rogers, C. J., and R. Allen. 1978. Developing Technology for Detoxification of Pesticides and Other Hazardous Materials. In: Disposal and Decontamination of Pesticides, M. V. Kennedy, ed. ACS Symposium, Series 73, American Chemical Society, Washington, DC.

Roper, M., T. Stack, and R. A. Deitrich. 1976. Phenobarbital and Tetrachlordibenzo-*p*-Dioxin Induce Different Isoenzymes of Aldehyde Dehydrogenase. Fed. Proc. 35:282.

Rose, J. Q., et al. 1976. The Fate of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Following Single and Repeated Oral Doses to the Rat. Toxicol. Appl. Pharmacol., 36:209–226.

Rosen, J. D. 1971. Photodecomposition of Organic Pesticides. In: Organic Compounds in Aquatic Environments, S. J. Faust and J. V. Hunter, eds. Marcel Dekker, Inc., NY.

Saint-Ruf, G. 1978. The Structure and Biochemical Effects of TCDD. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallaro, and G. Galli, eds. SP Medical and Scientific Books, NY.

Saint-Ruf, G., and Do-Phuoc Hien. 1975. Similarity of the Biochemical Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin and the 2,3,7,8-Tetrabromodibenzo-*p*-Dioxin in the Rat. C.R. Hebd. Seances Acad. Sci. Paris Ser. D, 280(23):2709–2711.

Salkinoja-Salonen, M. 1979a. Waste Purifying Procedure. U.S. Patent No. 4,169,049, September 25.

Salkinoja-Salonen, M. 1979b. Microbial Dechlorination of Chloro-Organics. University of Helsinki, Finland. Presentation given at U.S. EPA offices, IERL-Ci, December 11.

Sandermann, W., H. Stockmann, and R. Casten. 1957. Pyrolysis of Pentachlorophenol. Ber., 90:690.

Schantz, S. L., et al. 1979. Toxicological Effects Produced in Nonhuman Primates Chronically Exposed to Fifty Parts per Trillion 2,3,7,8-TCDD. Toxicol. Appl. Pharmacol., 48(1):A180.

Schwetz, B. A., P. J. Gehring, and R. J. Kociba. 1978. Toxicological Properties of Pentachlorophenol Relative to Its Content of Chlorinated Dibenzo-*p*-Dioxins. Dow Chemical, Midland, Michigan.

Schwetz, B.A., P.A. Keeler, and P.J. Gehring. 1973. The Effect of Purified and Commercial Grade Pentachlorophenol on Rat Embryonal and Fetal Development. Toxicol. Appl. Pharmacol., 28:146–150.

Schwetz, B. A., et al. 1973. Toxicology of Chlorinated Dibenzo-*p*-Dioxins. Environmental Health Perspectives, 5:87–99.

Science. 1979. Agent Orange Furor Continues to Build. Vol. 205, August 24.

Sconce, J.S., ed. 1967. Chlorine: Its Manufacture, Properties and Uses. Reinhold Publishing Corp., NY, pp. 448–456, and 851–852.

Scurlock, A.C., et al. 1975. Incineration in Hazardous Waste Management. U.S. Environmental Protection Agency, NTIS PB-261 049.

Seefeld, M.D., et al. 1979a. Effects of TCDD on Liver Function in Rats, Rabbits and Guinea Pigs. Toxicol. Appl. Pharmacol., 48(1):A153.

Seefeld, M.D., et al. 1979b. Time Course of TCDD Effects on Liver Function in Rhesus Monkeys. Toxicol. Appl. Pharmacol., 48(1):A160.

Seiler, J.P. 1973. A Survey on the Mutagenicity of Various Pesticides. Experientia, 29(5):622–623.

Seiler, J.P. 1977. Inhibition of Testicular DNA Synthesis by Chemical Mutagens and Carcinogens. Preliminary Results in the Validation of a Navel Short Term Test. Mutation Res., 46:305–310.

Severo, R. 1979. Agent Orange: A Legacy of Suspicion. The New York Times, May 27–29.

Shadoff, L.A., et al. 1977. The Gas Chromatographic-Mass Spectrometric Determination of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Fat from Cattle Fed Ronnel Insecticide. Ann. Chim., 67:583–592.

Shadoff, L.A., et al. 1977b. A Search for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in an Environment Exposed Annually to 2,4,5-Trichlorophenoxyacetic Acid Ester (2,4,5-T) Herbicide. Bulletin of Env. Contam. and Tox., 18:478, 197.

Sharma, R.P. 1978. Reversal of Immunologic and Toxicologic Effects of a Single Exposure of TCDD in Mice. Trace Subst. Environ. Health, 12:299–306.

Shea, K.P., and B. Lindler. 1975. Pandora and the Storage Tank. Environment, 17(6):12–15, September.

Shiroishi, K. 1978. EPA Office of Enforcement, personal communication. September 12.

Shiver, J.K. 1976. Converting Chlorohydrocarbon Wastes by Chlorolysis, EPA-600/2-76-270.

Short, F.W., and E.F. Elslager. 1962. Intestinal Anthelmintics. I. The Preparation of Bis-(2,4,5-Trichlorophenol), Piperazine Salt (Trichlofenol Piperazine) and Other Phenol-Piperazine Salts. J. Med. Pharm. Chem., 5:642.

Sidwell, A.E. 1976a. Chemistry of 2,4,5-T Production, and History of Trichlorophenol and 2,4,5-T Acid Manufacturers at Jacksonville, Arkansas. Written communications to the Arkansas Dept. of Pollution Control and Ecology, from Transvaal Inc., Jacksonville, Arkansas. September 17.

Sidwell, A.E. 1976b. TCDD Content of Soil and Liquid Sample. Written communication to T. Bennett, Jr., Transvaal, Inc., from Transvaal, Inc. October 27.

Sittig, M. 1969. Organic Chemical Process Encyclopedia, 2d ed. Noyes Data Corporation, Park Ridge, NJ.

Sittig, M., 1974. Pollution Control in the Organic Chemical Industry. Noyes Data Corporation, Park Ridge, NJ, pp. 116–119.

Sittig, M., ed. 1977. Pesticide Process Encyclopedia. Noyes Data Corporation, NJ.

Smith, F.A., B.A. Schwetz, and K.D. Nitchke. 1976. Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in CF-1 Mice. Toxicol. Appl. Pharmacol., 38: 517–523.

Solch, J.G., et al. 1978a. The Analysis of Environmental Samples for 2,3,7,8-TCDD Utilizing High and Low Resolution Gas-Liquid Chromatography-Mass Spectrometry. Final Report. U.S. EPA Contract No. 68-01-1959. June.

Solch, J.G., et al. 1978b. Development of GC-MS Methodology for Assaying Bovine Tissue for Hexa- , Hepta- , and Octachlorodibenzo-*p*-Dioxin Content. Proceedings of the 26th Annual Conference on Mass Spectrometry and Allied Topics, pp. 52–54.

Solch, J.G., et al. 1979. A Unique Scan Circuit for Use in Multiple Ion, GC-High Resolution MS Determination of Picogram Quantities of Chlorodioxins. Proceedings of the 27th Annual Conference on Mass Spectrometry and Allied Topics. In Press.

Solch, J.G., et al. 1980. Wright State University Quarterly Report to the U.S. EPA on Cooperative Agreement No. CR 806846-01. March 23.

Sparschu, G.L., F.L. Dunn, and V.K. Rowe. 1970. Teratogenic Study of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in the Rat. Toxicol. Appl. Pharmacol., 17:317–318.

Sparschu, G.L., F.L. Dunn, and V.K. Rowe. 1971. Study of the Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in the Rat. Fd. Cosmet. Toxicol., 9:405–412.

Stanford Research Institute. 1968–1969, 1971–1973, 1976–1979. Directory of Chemical Producers, USA. Menlo Park, California.

Stark, H.E., J.K. McBride, and G.F. Orr. 1975. Soil Incorporation/Biodegradation of Herbicide Orange. Vol. I. Microbial and Baseline Ecological Study of the U.S. Air Force Logistics Command Test Range, Hill Air Force Base, Utah. Final Report.

Stehl, R.H., and L.L. Lamparski. 1977. Combustion of Several 2,4,5-T Compounds: Formation of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Science, 197: 1008–1009.

Stehl, R.H., et al. 1973. The Stability of Pentachlorophenol and Chlorinated Dioxin to Sunlight, Heat and Combustion. In: Chlorodioxin—Origin and Fate. E.H. Blair, ed. American Chemical Society, Washington, DC. pp. 119-125.

Storherr, R.W., et al. 1971. Steam Distillation Technique for the Analysis of 2,3, 7,8-Tetrachlorodibenzo-*p*-Dioxin in Technical 2,4,5-T. J. Assoc. Off. Anal. Chem., 54:218-219.

Strigini, P. and A. Torriani. 1977. Seveso: "Encouraging Evidence?" Science, 197: 1034, 1036, September 9.

Sugar, J. 1979. Research Related to the Herbicide Buvinol, Especially for Possible Carcinogenicity. TARC Sci. Publ., 25:167-172.

Sugar, J., et al. 1979. Role of Pesticides in Hepatocarcinogenesis. J. Toxicol. Environ. Health, 5:1552-1553, pp. 183-191.

Sweeney, G.D. 1979. Iron Deficiency Prevents Liver Toxicity TCDD. Science, 204(4390):332-335.

Taylor, J.S. 1974. Chloracne—A Continuing Problem. Cutis, 13(585):4174.

Taylor, M. 1980. Personal communication. The Brehm Laboratory, Wright State University. March 4.

Taylor, M.L. and T.O. Tiernan. 1979. Written communication to L. Barnes, American Public Health Association, Washington, D.C. 20036. April 4.

Taylor, M.L., B.M. Hughes, and T.O. Tiernan. 1974a. GC-MS Procedures for Characterization of Herbicide Orange. Disposal of Herbicide Orange. USAF Environmental Health Laboratories, Brooks Air Force Base, Texas.

Taylor, M.L., B.M. Hughes, and T.O. Tiernan. 1974b. Preliminary Results Obtained with New GC-MS Procedures Developed for Determining Tetrachlorodibenzo-*p*-Dioxin in Chlorophenoxy Herbicides. Dioxin Planning Conference, EPA, Washington, DC.

Taylor, M.L., B.M. Hughes, and T.O. Tiernan. 1974c. Techniques for Analysis of Dioxin in Chlorophenoxy Herbicides. Status of Herbicide Orange Disposition, USAF Environmental Health Laboratories, Brooks Air Force Base, Texas.

Taylor, M.L., T.O. Tiernan, and B.M. Hughes. 1974. USAF Analytical Methodology Developed for Characterization of Herbicide Orange, EPA, Washington, DC.

Taylor, M.L., T.O. Tiernan, and B.M. Hughes. 1975. Analytical Techniques for Determination of Chlorodioxins. Proceedings, 1975 International Controlled Released Pesticide Symposium, pp. 401-406.

Taylor, M.L., J.G. Solch, and T.O. Tiernan. 1979. Advances in Analytical Methodology for Ultratrace Analysis of Tetrachlorodibenzo-*p*-Dioxin, Presented at the Dioxin Implementaiton Plan Collaborators' Meeting, January.

Taylor, M.L., et al. 1973. Determination of Trace Quantities of Chlorophenoxy-Type Herbicides and Related Chlorinated Residues in Soil Using GC-MS Techniques. Proceedings of the 21st Annual Conference on Mass Spectrometry and Allied Topics, pp. 336-339.

Taylor, M.L., et al. 1975. Determination of Tetrachlorodibenzo-*p*-Dioxin in Chemical and Environmental Matrices. Proceedings of the 23rd Annual Conference on Mass Spectrometry and Allied Topics, pp. 337-340.

Taylor, M.L., et al. 1976. Levels of Tetrachlorodibenzo-*p*-Dioxin in Environmental and Biological Samples as Determined by Gas Chromatography-High Resolution Mass Spectrometry. Proceedings of the 24th Annual Conference on Mass Spectrometry and Allied Topics, p. 595.

Techini, M.L., et al. 1977. Approaches to Examination of Genetic Damage after A Major Hazard in Chemical Industry: Preliminary Cytogenic Findings on TCDD-exposed Subjects after Seveso Accident. Presented at the Expert Conference on Genetic Damage Caused by Environmental Factors, Oslo, Norway, May 11–13.

Tenzer, R., et al. Characteristics of the Mobile Field Use System for the Detoxification/Incineration of Residuals from Oil and Hazardous Material Spill Clean-Up Operations. Prepared for U.S. Environmental Protection Agency by MBA Associates under Contract No. 68-03-2515.

Theiss, A.M., and P. Goldman. 1977. Uber das Trichlorphenol-Dioxin-Umfall-Geschehen um der BASF AG VOM 13 November 1953. In: Vortrag auf dem IV Medichem-Kongress, Haifa, 1976. International Agency for Research on Cancer.

Thigpen, J.E., et al. 1975. Increased Susceptibility to Bacterial Infection as a Sequel of Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Infection and Immunity, 12:1319–1324.

Thomas, P.T., and R. Hinsdill. 1979. The Effect of Perinatal Exposure to TCDD on the Immune Response of Young Mice. Drug. Chem. Tox. 2 Iss., 1–2:77–98.

Thomas Register of American Manufacturers. 1977. 67th ed., Vol. 8, Thomas Publishing Co.

Tiernan, T.O. 1975a. Analytical and Chemical Support for Herbicide Disposition Activities. Final Report. U.S. Air Force Contract No. F41608-76-C-0464.

Tiernan, T.O. 1975b. Applications of Mass Spectrometric Techniques for Pesticide Characterization, and Monitoring Environmental Effects. International Controlled Release Pesticide Symposium.

Tiernan, T.O. 1976. The Analysis of Environmental Samples for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Utilizing High and Low Resolution Gas-Liquid Chromatography-Mass Spectrometry. Final Report. U.S. EPA Contract No. 68-01-1959.

Tiernan, T.O., and M.L. Taylor. 1978. Development and Application of Analytical Methodology for Determination of Hexa-, Hepta-, and Octachlorodibenzodioxins in Beef Samples. Final Report. USDA Contract No. 12-64-4-378.

Tiernan, T.O., and M.L. Taylor. 1980. Interim Report on EPA Order No. D2832NAEX. March 31.

Tiernan, T.O., M.L. Taylor, and B.M. Hughes. 1975. Measurement of Tetrachlorodibenzo-*p*-Dioxins in USAF Herbicide Stocks and in Environmental Samples. 6th Annual Symposium on Environmental Research, Edgewood Arsenal, Maryland.

Tiernan, T.O., et al. 1979a. Methodology for Gas Chromatographic-High Resolution Mass Spectrometric Determination of Chlorodioxins in Complex Samples. 11th Ohio Valley Chromatography Symposium.

Tiernan, T.O., et al. 1979b. Determination of Tetrachlorodibenzo-*p*-Dioxin (TCDD) in Stack Effluent Samples Obtained During At-Sea Incineration of Herbicide Orange. U.S. EPA Purchase Order No. DA-8-6414J. May 31.

Tiernan, T.O., et al. 1980. Analyses of Industrial Samples for Tetrachlorodibenzo-*p*-Dioxins (TCDDs). Final Report. U.S. EPA Contract No. 68-03-2830 and Order Nos. 9T-1501-NTEX and OT-0267-NAEX. April 1.

Tomita, M. 1932. Synthesis of Diphenylene Dioxide. J. Pharm. Soc. Japan, 52: 429. Chemical Abstracts, 26:4589.

Tomita, M. 1933. Synthesis of Diphenylene Dioxide Derivatives. III. J. Pharm. Soc. Japan, 53:775. Chemical Abstracts, 28:3391, 1934.

Tomita, M. 1935. Synthesis of Diphenylene Dioxide Derivatives. VI. The Nitration of Diphenylene Dioxide. J. Pharm. Soc. Japan, 55:1060. Chemical Abstracts, 31:6661, 1937.

Tomita, M. 1936. Synthesis of Diphenylene Dioxide Derivatives. IX. Ring Closure of the Diphenylene Dioxide Nucleus. J. Pharm. Soc. Japan, 56:814. Chemical Abstracts, 32:8426, 1938.

Tomita, M. 1937. Synthesis of Diphenylene Dioxide Derivatives. XII. Friedel-Crafts Reaction on Diphenylene Dioxide. J. Pharm. Soc. Japan, 57:609. Chemical Abstracts, 33:2898.

Tomita, M., and C. Tani. 1942. Synthesis of Dibenzo -*p*-Dioxin Derivatives. XVI. General Synthetic Method for Diphenylene Oxide Derivatives. J. Pharm. Soc. Japan, 62:476. Chemical Abstracts, 45:5146, 1951.

Tomita, M., and J. Yagi. 1958. Dibenzo-*p*-Dioxin Derivatives. XXIV. Friedel-Crafts Reaction of Dibenzo-*p*-Dioxin Derivatives. Yakugaku Zasshi, 78:581. Chemical Abstracts, 52:18421, 1958.

Tomita, M., T. Nakano, and K. Hirai. 1954. Synthesis of Diphenylene Dioxide XXI. J. Pharm. Soc. Japan, 74:934. Chemical Abstracts, 49:10964, 1955.

Tomita, M., S. Ueda, and M. Narisada. 1959. Dibenzo-*p*-Dioxin Derivatives. XXVII. Synthesis of Polyhalodibenzo-*p*-Dioxin. Yakugaku Zasshi, 79:186. Chemical Abstracts, 53:13152, 1959.

Ton That, T., et al. 1973. Le Cancer Primaire du Foie au Viet-Nam. Chirurgie International Agency for Research on Cancer, 99:427–436.

Toth, K., et al. 1977. Carcinogenic Bioassay of the Herbicide 2,4,5-Trichlorophenoxy Ethanol (TCPE) with Different 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Dioxin) Content in Swiss Mice. In: International Conference on Ecological Perspectives on Carcinogens and Cancer Control, Basel and Karger, eds., Cremona, 1976.

Toth, K., et al. 1979. Carcinogenicity Testing of Herbicide 2,4,5-T Ethanol Containing Dioxin and of Pure Dioxin in Swiss Mice. Nature, 278(5704):548–549.

Toxic Materials News. 1979a. Toxic Materials News in Brief. 6(9):70, February 28.

Toxic Materials News. 1979b. Remaining Uses of 2,4,5-T, Silvex Undergo Review Prior to Possible Cancellation. July 18, p. 230.

Toxic Materials News. 1979c. Toxic Materials News in Brief. July 25, p. 239.

Toxic Materials News. 1979d. Federal Judge Allows Agent Orange Suit Against Manufacturers. 6(48):381, November 28.

Toxic Materials News. 1979e. Toxic Materials News in Brief. November 28, p. 383.

Ueda, S. 1962. Dibenzo-*p*-Dioxin Derivatives. XXXI. Synthesis of Polyhalodibenzo-*p*-Dioxin. Yakugaku Zasshi, 83:714.

Ueda, S. 1963. Dibenzo-*p*-Dioxin (Diphenylene Dioxide) Derivatives. XXXVI. Methylation Product of Dibenzo-*p*-Dioxin. Yakugaku Zasshi, 83:802.

Ueda, S., and T. Akio. 1963. Dibenzo-*p*-Dioxin (Diphenylene Dioxide) Derivatives. XXXIII. Substitution Reaction of 1,6-Dimethoxydibenzo-*p*-Dioxin and 1,6-Dibromodibenzo-*p*-Dioxin. Yakugaku Zasshi, 83:552.

Ueo, S. 1941. 2,6-Dichlorodiphenylene Dioxide. Bull. Chem. Soc. Japan, 16:177.

Ullmann, F. 1903. Uber eine neue Bildungweise von Diphenylaminderivaten. Ber., 36:2382.

U.S. Code of Federal Regulations Title 21. 1978. Subpart D, Section 250.250. Hexachlorophene, as a component of drug and cosmetic products. Effective January 19, 1978.

U.S. Dept. HEW. 1975. Center for Disease Control, NIOSH. Health Hazard Evaluation Determination Report No. 74-117-251, December.

U.S. Dept. HEW. 1978. Bioassay of Hexachlorophene for Possible Carcinogenicity. National Cancer Institute. Carcinogenesis Technical Report. CAS No. 70-30 NCI-CG-TR-40, Series No. 40, p. 1.

U.S. Environmental Protection Agency. 1975a. Destructing Chemical Wastes in Commercial Scale Incinerators. Volume I, Technical Summary. July. NTIS PB-257 709.

U.S. Environmental Protection Agency. 1975b. Hazardous Waste Disposal Damage Reports. Document No. 2. EPA/530/SW- 151.2.

U.S. Environmental Protection Agency. 1977a. Destroying Chemical Wastes in Commercial Scale Incinerators, Facility Number 1—The Marquat Company. NTIS PB-265 451.

U.S. Environmental Protection Agency. 1977b. NAS. Drinking Water and Health, PB-269519.

U.S. Environmental Protection Agency. 1978a. Ambient Water Quality Criteria 2,3,7,8-TCDD. Washington, DC.

U.S. Environmental Protection Agency. 1978b. Computer Data Files on Priority Pollutants in the Leather-Tanning Industry, Lines 2261-8615. Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1978c. Draft Report of the Ad Hoc Study Group on Pentachlorophenol Contaminants. Environmental Health Advisory Committee, Science Advisory Board. Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1978d. Draft Status Report. Dioxin in Industrial Sludges. Office of Solid Waste, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1978e. Notice of Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing Pentachlorophenol. Federal Register, 43(202):48443-48617.

U.S. Environmental Protection Agency. 1978f. Pesticide Product Information on Microfiche, Chemical Reference File (Alpha). Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1978g. Phase I Report on Hexachlorobenzene (HCB). Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1978h. Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing 2,4,5-T. Federal Register, 43(78):17116-17157.

U.S. Environmental Protection Agency. 1978i. Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing 2,4,5-Trichlorophenol and Its Salts. Federal Register, 43(149):34026-34054.

U.S. Environmental Protection Agency. 1979. The Presence of Priority Pollutants in the Synthetic Manufacture of Pharmaceuticals. Draft.

U.S. International Trade Commission. 1974, 1976, 1977. Synthetic Organic Chemicals, United States Production and Sales.

U.S. National Institute of Environmental Health Sciences/International Agency for Research on Cancer. 1978. Long-Term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans. Joint Working Group Report, IARC, Lyon, France.

U.S. Patent Office. 1935. Patent No. 1,991,329. Alkali Metal Trichlorophenolates.

U.S. Patent Office. 1939. Patent No. 2,176,417. Preparation of Pentachloro phenol.

U.S. Patent Office. 1941. Patent No. 2,250,480. Dihydroxy Hexachloro Diphenyl Methane and Methods of Producing the Same.

U.S. Patent Office. 1943. Patent No. 2,319,960. Process for Producing Halogenated Cresols.

U.S. Patent Office. 1948. Patent No. 2,435,593. Process for Making Bis-(3,5,6-Trichloro-2-hydroxyphenyl) Methane.

U.S. Patent Office. 1949. Patent No. 2,471,575. Process of Preparing 2,4-Dichlorophenoxyacetic Acid.

U.S. Patent Office. 1950. Patent No. 2,509,245. Preparation of 2,4,5-Trichlorophenol.

U.S. Patent Office. 1952. Patent No. 2,599,516. *O*-2,4,5-Trichlorophenyl *O,O*-Dialkyl-Thiophosphates.

U.S. Patent Office. 1955a. Patent No. 2,703,322. Poly Halo-Salicylanilides.

U.S. Patent Office. 1955b. Patent No. 2,728,799. Refinement of Benzene Hexachloride.

U.S. Patent Office. 1956a. Patent No. 2,749,360. Esters of α-2,4,5-Trichlorophenoxy-Propionic Acid.

U.S. Patent Office. 1956b. Patent No. 2,754,324. α- α-Dichloropropionates of the Haloaryloxy Lower Alkanols.

U.S. Patent Office. 1956c. Patent No. 2,756,260. Method of Making Trichlorophenol Mixtures Which Are Rich in the 2,4,5-isomer.

U.S. Patent Office. 1956d. Patent No. 2,765,224. Herbicide.

U.S. Patent Office. 1957a. Patent No. 2,792,434. Process for the Production of Hexachlorobenzene.

U.S. Patent Office. 1957b. Patent No. 2,799,713. Method of Making Trichlorophenols from Tetrachlorobenzenes.

U.S. Patent Office. 1957c. Patent No. 2,799,714. Method of Hydrolyzing Di- and Trichlorobenzenes.

U.S. Patent Office. 1957d. Patent No. 2,812,365. Process of Preparing Bis-(3,5,6-Trichloro-2-Hydroxyphenyl) Methane.

U.S. Patent Office. 1957e. Patent No. 2,812,366. Improvements in the Preparation of Polychlorophenols.

U.S. Patent Office. 1957f. Patent No. 2,812,367. Improvements in the Preparation of Polychlorophenols in Aqueous Medium.

U.S. Patent Office. 1958a. Patent No. 2,830,083. Production of Aryloxy Aliphatic Carboxylic Acids.

U.S. Patent Office. 1958b. Patent No. 2,849,494. 2,2,-Thiobis (Polyhalophenols).

U.S. Patent Office. 1958c. Patent No. 2,852,548. Process for the Production of Salts of Aryloxyalkanol-Sulfuric Acid Semiesters.

U.S. Patent Office. 1960a. Patent No. 2,922,811. Method for the Manufacture of *O*-(Chlorophenyl)*O,O*-dialkylphosphorothiolates.

U.S. Patent Office. 1960b. Patent No. 2,947,790. Process for the Manufacture of *O*-(Chlorophenyl)*O,O*-Dialkylphosphorothiolates.

U.S. Patent Office. 1961a. Patent No. 2,980,681. Salt of Piperazine and 2,4,5-Trichlorophenol.

U.S. Patent Office. 1961b. Patent No. 3,005,720. Bacteriostatic Articles and Method of Manufacture.

U.S. Patent Office. 1962. Patent No. 3,024,163. Bacteriostats.

U.S. Patent Office. 1963a. Patent No. 3,074,790. Method for the Control of Undesired Vegetation.

U.S. Patent Office. 1963b. Patent No. 3,076,025. Process for Production of Substituted Phenoxyalkanoic Acid.

U.S. Patent Office. 1967a. Patent No. 3,297,427. Synergistic Herbicidal Composition and Method.

U.S. Patent Office. 1967b. Patent No. 3,347,937. 2,4,5-Trichlorophenol.

U.S. Patent Office. 1969. Patent No. 3,481,991. Preparation of Chlorinated Hydroxy Compounds.

U.S. Patent Office. 1971. Patent No. 3,607,949. Production of 2,2-Methylenebis-(3,4,6-Trichlorophenol).

U.S. Patent Office. 1972. Patent No. 3,676,508. Process of the Manufacture of Carbon Tetrachloride.

U.S. Patent Office. 1974a. Patent No. 3,816,268. Stabilized Distillation of Pentachlorophenol.

U.S. Patent Office. 1974b. Patent No. 3,852,160. Distillation of Pentachlorophenol with Salicylaldehyde and Water.

U.S. Patent Office. 1974c. Patent No. 3,852,161. Distillation of Pentachlorophenol.

U.S. Tariff Commission. 1968. Synthetic Organic Chemicals, United States Production and Sales.

Van Miller, J.P., and J.R. Allen. 1977. Chronic Toxicity of 2,3,7,8-TCDD in Rats. Fed. Am. Soc. Exp. Biol., 35:396.

Van Miller, J.P., J.J. Lalich, and J.R. Allen. 1977. Increased Incidence of Neoplasms in Rats Exposed to Low Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. Chemosphere, 6:537–544.

Van Miller, J.P., R.J. Marlar, and J.R. Allen. 1976. Tissue Distribution and Excretion of Tritiated Tetrachlorodibenzo-*p*-Dioxin in Nonhuman Primates and Rats. Fd. Cosmet. Toxicol., 14:31–34.

Verrett, J. 1970. Statement of Dr. J. Verrett, Food and Drug Administration, Department of HEW. In:Hearings before the Subcommittee on Energy, Natural Resources and the Environment of the Committee on Commerce, U.S. Senate, Second Session, on Effects of 2,4,5-T on Man and the Environment. Serial 96-60, pp. 190–203.

Villanueva, E.C., V.W. Burse, and R.W. Jennings. 1973. Chlorodibenzo-*p*-Dioxins Contamination of Two Commercially Available Pentachlorophenols. J. Agric. Food Chem., 21(4):739–740.

Villanueva, E.C., et al. 1974. Evidence of Chlorodibenzo-*p*-Dioxin and Chlorodibenzofuran in Hexachlorobenzene. J. Agric. Food Chem., 22(5):916–917.

Vinopal, J.H., and J.E. Casida. 1973. Metabolic Stability of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Mammalian Liver Microsomal Systems and in Living Mice. Arch. Environ. Contam. Toxicol., 1:122–132.

Vinopal, J.H., I. Yamamoto, and J.E. Casida. 1973. Preparation of Tritium-Labeled Dibenzo-*p*-Dioxin and 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. In: Chlorodioxins—Origin and Fate, E.H. Blair, ed. American Chemical Society, Washington, DC.

Viviani, A., et al. 1978. Time Course of the Induction of Aryl Hydrocarbon Hydroxylase in Rat Liver Nuclei and Microsomes by Phenobarbital, 3-Methyl Cholanthrene, TCDD, Dieldrin and Other Inducers. Biochemical Pharmacology, 27:2103–2108.

Vos, J.G., and L. Kater. 1978. Immune Suppression by TCDD. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallaro, and G. Galli, eds. SP Medical and Scientific Books, NY.

Vos, J.G., and J.A. Moore. 1974. Suppression of Cellular Immunity in Rats and Mice by Maternal Treatment with 2,3,7,8-TCDD. Int. Arch. Allergy Appl. Immunol., 47:777–779.

Vos, J.G., J.A. Moore, and J.G. Zinkl. 1973. Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin on the Immune System of Laboratory Animals. Environmental Health Perspectives, 5:149–162.

Vos, J.G., J.A. Moore, and J.G. Zinkl. 1974. Toxicity of 2,3,7,8-TCDD in C57Bl/6 Mice. Toxicol. Appl. Pharmacol., 29:229–241.

Vos, J.G., et al. 1978. Studies on 2,3,7,8-TCDD-Induced Immune Suppression and Decreased Resistance to Infection: Endotoxin Hypersensitivity, Serum Zinc Concentrations and Effects of Thymosin Treatment. Toxicology, 9:75–86.

Wade, N. 1971. Hexachlorophene: FDA Temporizes on Brain Damaging Chemical. Science, 174:805–807.

Walker, A.E., and J.V. Martin. 1979. Lipid Profiles in Dioxin-Exposed Workers. Lancet, 446–447, February 29.

Wall Street Journal. 1979. EPA Orders Immediate Halt to Most Uses of Herbicide 2,4,5-T and Similar Products. March 2.

Walsh, J. 1977. Seveso—The Questions Persist Where Dioxin Created a Wasteland. Science, 197:1064–1067.

Ward, C., and F. Matsumura. 1977. Fate of 2,4,5-T Contaminant, 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in Aquatic Environments. Department of Entomology, University of Wisconsin. Technical Completion Report, Project Number OWRT-A-058-Wis.

Ward, C.T., and F. Matsumara. 1978. Fate of 2,3,7,8-TCDD in a Model Aquatic Environment. Arch. Environ. Contam. Toxicol., 7(3):349–357.

Warnick, H. 1977. Memorandum to U.S. Environmental Protection Agency File. Representative 2,4,5-T Labels. Research Triangle Park, NC.

Warnick, H. 1978a. EPA Office of Pesticide Programs, personal communication. August 21.

Warnick, H. 1978b. EPA Office of Pesticide Programs, personal communications. October 20.

Wassom, J.S., H.E. Huff, and N. Loprieno. 1978. A Review of the Genetic Toxicology of Chlorinated Dibenzo-*p*-Dioxins. Draft Report. National Inst. of Environ. Health Sciences, Interagency Agreement 40-247-70.

Watkins, D.A. 1974. Implications of the Photochemical Decomposition of Pesticides. Chemistry and Industry (London), 5:185–190.

Watkins, D.R. 1978b. Program for Prevention of Dioxin Exposure. U.S. EPA, IERL-Cincinnati, Ohio. Unpublished.

Watkins, D.R. 1979a. History of Industrial Sample Containing Dioxin (TCDD's). U.S. EPA, IERL-Cincinnati memo. March 27.

Watkins, D.R. 1979b. Personal communication. U.S. EPA, Environmental Research Laboratory, Cincinnati, Ohio.

Watkins, D.R. 1980. Personal communication. U.S. EPA, IERL-Cincinnati, Ohio.

Webber, T.J.N., and D.G. Box. 1973. The Examination of Tetrachlorvinphos and Its Formulations for the Presence of Tetrachlorodibenzo-*p*-Dioxins by a Gas-Liquid Chromatographic Method. Analyst (London), 98:181.

Weissberg, J.B., and J.G. Zinkl. 1973. Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin upon Hemostasis and Hematologic Function in the Rat. Environmental Health Perspectives, 5:119–123.

Weitzman, L. n.d. The Utility of Wet Oxidation in the Treatment of Hazardous Organic Wastes. Michigan Technological University Grant Proposal. Memorandum to Dr. E. Berdau, U.S. EPA, IERL-Cincinnati.

Wertheim, E. 1939. Textbook of Organic Chemistry. The Blakiston Co., Philadelphia, PA.

Westing, A.H. 1979. The Safety of 2,4,5-T. Science, 206:1135, December.

WGBH Educational Foundation. 1979. A Plague on Our Children. *NOVA* Transcript.

Whitemore, F.C. 1975. A Study of Pesticide Disposal in a Sewage Sludge Incinerator. EPA/530/SW116c, NTIS PB-253 485.

Whiteside, T. 1977. A Reporter at Large: The Pendulum and the Toxic Cloud. The New Yorker, July 25, pp. 30–55.

Wilkinson, R.R., G.L. Kelso, and F.C. Hopkins. 1978. State-of-the-Art Report: Pesticide Disposal Research. EPA-600/2-78-183.

Wilkinson, R.D., et al. 1978. State-of-the-Art Report on Pesticide Disposal Research. In: Disposal and Decontamination of Pesticides, M.V. Kennedy, ed. ASC Symposium Series 73, American Chemical Society, Washington, DC, pp. 73–80.

Williams, D.T., and B.J. Blanchfield. 1971. Thin Layer Chromatographic Separation of Two Chlorodibenzo-*p*-Dioxins from Some Polychlorinated Biphenyls and Organochlorine Pesticides. Journal of the AOAC, 55:1429–1431.

Williams, D.T., and B.J. Blanchfield. 1972. Screening Method for the Detection of Chlorodibenzo-*p*-Dioxins in the Presence of Chlorobiphenyls, Chloronaphthalenes, and Chlorodibenzofurans. Journal of the AOAC, 55:93–95.

Wilson, J. 1978. Breast Enlargement at an Italian School. Lancet, 1(8066):772.

Windholz, M., ed. 1976. Merck Index, 9th Ed., Merck & Co., Inc. Rahway, NJ.

Wipf, H.K., et al. 1978. Field Trials of Photodegradation of TCDD on Vegetation after Spraying with Vegetable Oil. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallero, and G. Galli, eds. SP Medical and Scientific Books, NY, pp. 201–216.

Wong, A.S., and D.G. Crosby. 1978. Decontamination of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) by Photochemical Action. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallero, and G. Galli, eds. SP Medical and Scientific Books, NY.

Woods, J.S. 1973. Studies of the Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin of Mammalian Hepatic S-aminolevulinic Acid Synthetase. Environmental Health Perspectives, 5:221–225.

Woolson, E. A., and P. D. Ensor. 1973. Dioxin Residues in Lakeland Sand and Bald Eagle Samples. In: Chlorodioxins—Origin and Fate, E. Blair, ed. American Chemical Society, Washington, DC, pp. 112–118.

Woolson, E. A., R. F. Thomas, and P. D. Ensor. 1972. Survey of Polychlorodibenzo-*p*-Dioxin Content in Selected Pesticides. J. Agric. Food Chem., 20(2): 351–354.

World Health Organization. 1977. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. Vol. 15, Lyon, France, August.

World Health Organization. 1978. International Agency for Research on Cancer. Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity. No. 7, Lyon, France.

Wright State University. 1976. Annual Report on U.S. EPA Contract No. 68-01-1959. The Analysis of Environmental Samples for TCDD Utilizing High and Low Resolution Gas-Liquid Chromatograph-Mass Spectrometry. EPA Office of Special Pesticide Reviews, Washington, DC.

Wright State University. 1979a. Report on Analyses of Love Canal Samples for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD). New York State Department of Health Purchase Order No. 5975. January 21.

Wright State University. 1979b. Report on Analyses of Love Canal Samples for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD). For New York State Department of Health. April 20.

Yang, G.C., and A.E. Pohland. 1973. Cation Radicals of Chlorinated Dibenzo-*p*-Dioxins. In: Chlorodioxins—Origin and Fate, E. Blair, ed. American Chemical Society, Washington, DC, pp. 33–43.

Yang, K.H., and R.E. Peterson. 1979. Differential Effects of Halogenated Aromatic Hydrocarbons on Pancreatic Excretory Function in Rats. University of Wisconsin, Madison.

Yates, P.B. 1979. Written communication to D. R. Watkins, U.S. EPA, IERL-Cincinnati, from New South Wales State Pollution Control Commission, Australia, January 18.

Yelton, R.O., M.L. Taylor, and T.O. Tiernan. 1977. Ultrasensitive Method for Determination of Chlorodioxins in Commercially Produced Phenols. Proceedings for the 25th Annual Conference on Mass Spectrometry and Allied Topics, p. 595.

Yockim, R.S., A.R. Isensee, and G.T. Jones. 1978. Distribution and Toxicity of TCDD and 2,4,5-T in an Aquatic Model Ecosystem. Chemosphere, 7(3):215–220.

Young, A.L. 1974. Ecological Studies on a Herbicide-Equipment Test Area. (TA C-52A) Eglin Air Force Base Reservation, Florida. Air Force Armament Lab, Technical Report AFATL-TR-74-12.

Young, A.L. 1978. Written communication to D.R. Watkins, U.S. EPA, IERL-Cincinnati, from USAF. August 23.

Young, A.L., E. Arnold, and A.M. Wachinsk. 1974. Field Studies on the Soil Persistence and Movement of 2,4-D, 2,4,5-T and TCDD. Presentation to the Weed Science Society of America, Las Vegas, Nevada, Abstract No. 226, February 13.

Young, A.L., C.E. Thalken, and W.E. Ward. 1975. Studies of the Ecological Impact of Repetitive Aerial Applications of Herbicides on the Ecosystem of Test

Area C-52A, Eglin Air Force Base, Florida. A.F. Armament Lab. AFATL-TR-75-142.

Young, A. L., et al. 1976. Fate of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in the Environment: Summary and Decontamination Recommendations USAFA-TR-76-18.

Young, A.L., et al. 1978. The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and Its Associated Dioxin. USAF, OEHL Technical Report TR-78-92.

Zedda, S., A.M. Cirla, and C. Sala. 1976. Accidental Contamination by TCDD: The ICMESA Incident. Medicina Del Lavoro, 67(5):371-378.

Zinke, T. 1894. Uber die Einwirkung von Chlor auf Phenole. Ber., 27:550.

Zinkl, J.G., et al. 1973. Hematologic and Clinical Chemistry Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Laboratory Animals. Environmental Health Perspectives, 5:111-118.

Zitko, V., O. Hutzinger, and P.M. Choi. 1972. Contamination of the Bay of Fundy-Gulf of Maine Area with Polychlorinated Biphenyls, Polychlorinated Terphenyls, Polychlorinated Dibenzodioxins, and Dibenzofurans. Environmental Health Perspectives.

APPENDIX A

The tables that follow list organic chemicals and pesticides selected for study on the basis of potential dioxin contamination, with known producers and production locations, present and past. The primary source of producer information is the Stanford Research Institute Directory of Chemical Producers. The tabulations are by chemical, with producers and locations; and by producer and location, with chemicals. The tabulations by chemical (Tables A1, A2, A3, and A6) are segregated according to the classifications based on dioxin concern as defined in Section 3. The classification information is also noted in the producer location tables by means of Roman numerals following the chemical names.

The tabulations by producer and location (Tables A4 and A7) group all of the critical chemicals involved at each manufacturer location. These lists do not necessarily define the site subject to exposure, because many dumps are remote from the plants; they do provide a starting point for such definition. Abandoned production of a chemical or abandoned facilities may present special problems. Therefore, the production facilities noted since 1968 but no longer active in 1978 are footnoted and are also extracted in separate tables (Tables A5 and A8). Some of these sites remain active in other production, and some may retain production capability and/or minor production of the subject chemical. Other plant sites may be totally deactivated or abandoned. The producer listed is the last known operator.

Some of the company names of producers designate subsidiary or divisional names, with notation of the parent company. Company addresses, from the Stanford Research Institute Directory and from the Thomas Register, are for the last known producer at a given location and are subject to the uncertainties introduced by acquisitions and name changes.

TABLE A1. PRODUCERS OF CLASS I ORGANIC CHEMICALS

Chemical	Producer	Location
4-Bromo-2,5-dichlorophenol	Velsicol	Beaumont, TX
2-Chloro-4-fluorophenol	Olin	Rochester, NY
Decabromophenoxybenzene	Great Lakes Chem.	El Dorado, AR
2,4-Dibromophenol	Dow	Midland, MI
	White Chem.	Bayonne, NJ
2,3-Dichlorophenol	Specialty Organics	Irwindale, CA
	Aldrich	Milwaukee, WI*
	Diamond Shamrock	Newark, NJ*
2,4-Dichlorophenol	Dow	Midland, MI
	Monsanto	Sauget, IL
	Rhodia	Freeport, TX
	Transvaal	Jacksonville, AR
2,5-Dichlorophenol	Velsicol	Beaumont, TX
2,6-Dichlorophenol	Aldrich	Milwaukee, WI
	Specialty Organics	Irwindale, CA
3,4-Dichlorophenol	Aldrich	Milwaukee, WI
Pentabromophenol	Michigan Chem.	St. Louis, MI*
	R.S.A.	Ardsley, NY*
	White Chem.	Bayonne, NJ
2,4,6-Tribromophenol	Dow	Midland, MI*
	Eastern Chem.	Pequannock, NJ*
	Guardian	Hauppauge, NJ
		Pequannock, NJ*
	Velsicol	St. Louis, MI*
	R.S.A.	Ardsley, NY*
	White Chem.	Bayonne, NJ

*No longer produced at this location.

TABLE A2. PRODUCERS OF CLASS II ORGANIC CHEMICALS

Chemical	Producer	Location
Bromophenetole	R.S.A.	Ardsley, NY
o-Bromophenol	Eastman Kodak R.S.A.	Rochester, NY Ardsley, NY
2-Chloro-1,4-diethyoxy-5-nitrobenzene	Fairmount Chem. GAF Pfister	Newark, NJ Rensselaer, NY Newark, NJ*
5-Chloro-2,4-dimethoxyaniline	GAF Pfister	Rensselaer, NY Ridgefield, NJ Newark, NJ*
Chlorohydroquinone	Eastman Kodak Eastern Chem. Guardian	Rochester, NY Pequannock, NJ* Hauppauge, NY* Pequannock, NJ*
o-Chlorophenol	Dow Monsanto	Midland, MI Sauget, IL
2-Chloro-4-phenylphenol	Dow	Midland, MI
4-Chlororesorcinol	Am. Color & Chem. GAF	Lock Haven, PA Rensselaer, NY
2,6-Dibromo-4-nitrophenol	Martin Marietta Maumee Sherwin Williams	Sodyeco, NC* St. Bernard, OH* St. Bernard, OH*
3,5-Dichlorosalicylic acid	Aceto Inmont Corp.	Carlstadt, NJ Carlstadt, NJ*
2,6-Diiodo-4-nitrophenol	R.S.A.	Ardsley, NY
3,5-Diiodosalicylic acid	Morton Chem. R.S.A.	Ringwood, IL* Ardsley, NY*
o-Fluoroanisole	Olin	Rochester, NY
o-Fluorophenol	Olin	Rochester, NY
Tetrabromobisphenol-A	Dow Great Lakes Velsicol	Midland, MI El Dorado, AR St. Louis, MI
Tetrachlorobisphenol-A	Dover	Dover, OH*

*No longer produced at this location.

TABLE A3. PRODUCERS OF CLASS III ORGANIC CHEMICALS

Chemical	Producer	Location
3-Amino-5-chloro-2-hydroxybenzenesulfonic acid	Allied	Buffalo, NY*
	Nyanza	Ashland, MA
	Toms River Chem.	Toms River, NJ
2-Amino-4-chloro-6-nitrophenol	Nyanza	Ashland, MA
o-Anisidine	Am. Color and Chem.	Lock Haven, PA
	Am. Aniline	Lock Haven, PA*
	du Pont	Deepwater, NJ
	Monsanto	St. Louis, MO*
Benzaldehyde	Crompton and Knowles	Fair Lawn, NJ
	Dow	Kalama, WA*
	Fritzsche	Clifton, NJ*
	Kalama Chem.	Kalama, WA
	Monroe Chem.	Eddystone, PA
	F. Ritter	Los Angeles, CA*
	Stauffer	Edison, NJ*
		Nixon, NJ*
	Tenneco	Fords, NJ*
		Garfield, NJ
	UOP	East Rutherford, NJ
	Velsicol	Chattanooga, TN*
Bromobenzene	Dow	Midland, MI
	Velsicol	St. Louis, MI*
o-Bromofluorobenzene	Olin	Rochester, NY
o-Chlorofluorobenzene	Olin	Rochester, NY
3-Chloro-4-fluoronitrobenzene	Olin	Rochester, NY
3-Chloro-4-fluorophenol	Olin	Rochester, NY
4-Chloro-2-nitrophenol	du Pont	Deepwater, NJ*
	Maumee	St. Bernard, OH*
	Sherwin Williams	St. Bernard, OH*
Chloropentafluorobenzene	Whittaker	San Diego, CA*
2,4-Dibromofluorobenzene	Olin	Rochester, NY
3,4-Dichloroaniline	Blue Spruce	Bound Brook, NJ
		Edison, NJ*
	Chem. Insecticide	Metuchen, NJ*
	du Pont	Deepwater, NJ
	Martin Marietta	Sodyeco, NC*
	Monsanto	Luling, LA
		Sauget, IL*

(continued)

TABLE A3. (continued)

Chemical	Producer	Location
o-Dichlorobenzene	Allied	Syracuse, NY*
	Chem. Products	Cartersville, GA*
	Dover	Dover, OH*
	Dow	Midland, MI
	du Pont	Deepwater, NJ*
	Hooker	Niagara Falls, NY*
	Monsanto	Sauget, IL
	Montrose Chem.	Henderson, NV
	Neville Chem.	Santa Fe Springs, CA*
	Olin	McIntosh, AL*
	PPG	Natrium, WV
	Solvent Chem.	Niagara Falls, NY
		Malden, MA*
	Specialty Organics	Irwindale, CA
	Standard Chlorine	Delaware City, DE
		Kearny, NJ
3,4-Dichlorobenzaldehyde	Tenneco	Fords, NJ
3,4-Dichlorobenzotrichloride	Tenneco	Fords, NJ
3,4-Dichlorobenzotrifluoride	Tenneco	Fords, NJ*
1,2-Dichloro-4-nitrobenzene	Blue Spruce	Bound Brook, NJ
		Edison, NJ*
	Chem. Insecticide	Metuchen, NJ*
	Martin Marietta	Sodyeco, NC*
	Monsanto	Sauget, IL*
	Plastifax	Gulfport, MS
3,4-Dichlorophenylisocyanate	Mobay Chem.	New Martinsville, SC
	Ott Chem.	Muskegon, MI*
3,4-Difluoroaniline	Olin	Rochester, NY
o-Difluorobenzene	Olin	Rochester, NY
1,2-Dihydroxybenzene-3,5-disulfonic acid, disodium salt	Sterling Drug	New York, NY*
2,5-Dihydroxybenzenesulfonic acid	Eastman Kodak	Rochester, NY*
	Nease Chem.	State College, PA*
2,5-Dihydroxybenzenesulfonic, acid, potassium salt	Nease Chem.	State College, PA*
2,4-Dinitrophenol	Martin Marietta	Sodyeco, NC
	Mobay	Bushy Park, SC
2,4-Dinitrophenoxyethanol	Hummel Chem.	Newark, NJ*
		South Plainfield, NJ

(continued)

TABLE A3. (continued)

Chemical	Producer	Location
3,5-Dinitrosalicylic acid	Eastman Kodak	Rochester, NY
	Hummel Chem.	Newark, NJ*
		South Plainfield, NJ*
	Salsbury Labs	Charles City, IA
Fumaric acid	Allied	Buffalo, NY*
		Moundsville, WV*
	Alberta Gas	Duluth, MN
	Hooker	Arecibo, PR
	Monsanto**	St. Louis, MO
	Petro-Tex	Houston, TX*
	Pfizer	Terre Haute, IN
	Reichold	Morris, IL*
	Stepan Chem.	Fieldsboro, NJ*
	Tenneco	Garfield, NJ
	U.S. Steel	Neville Island, PA
Hexabromobenzene	Velsicol	St. Louis, MI
	Dover	Dover, OH*
Hexachlorobenzene	Hummel Chem.	Newark, NJ*
		South Plainfield, NJ*
	Stauffer	Louisville, KY*
Hexafluorobenzene	PCR	Gainesville, FL
	Whittaker	San Diego, CA*
		Louisville, KY*
Maleic acid	Allied	Buffalo, NY*
		Marcus Hook, PA
		Moundsville, WV*
	Eastman Kodak	Rochester, NY*
	Pfanstiehl Labs	Waukegan, IL
Maleic anhydride	Allied	Moundsville, WV*
	Amoco	Joliet, IL
	Asland	Neal, WV
	Chevron	Richmond, CA*
	Koppers	Bridgeville, PA
		Cicero, IL
	Petro-Tex	Houston, TX*
	Monsanto	St. Louis, MO
	Reichhold	Elizabeth, NJ
		Morris, IL
	Standard Oil of Indiana (see Amoco above)	
	Tenneco	Fords, NJ
	U.S. Steel	Neville Island, PA
o-Nitroanisole	du Pont	Deepwater, NJ
	Monsanto	Sauget, IL*
		St. Louis, MO

(continued)

TABLE A3. (continued)

Chemical	Producer	Location
2-Nitro-*p*-cresol	Sherwin Williams	Chicago, IL
	du Pont	Deepwater, NJ*
o-Nitrophenol	Monsanto	Sauget, IL
	du Pont	Deepwater, NJ
Pentabromochlorocyclohexane	Dow	Midland, MI
Pentabromoethylebenzene	Hexcel	Sayreville, NJ
Pentabromotoluene	White Chem.	Bayonne, NJ
Pentachloroaniline	Olin	Rochester, NY
Pentafluoroaniline	Whittaker	San Diego, CA*
o-Phenetidine	Am. Aniline	Lock Haven, PA*
	Monsanto	St. Louis, MO*
Phenol (from chlorobenzene)	Dow	Midland, MI*
	Hooker	North Tonawanda, NY* South Shore, KY*
	Union Carbide	Marietta, OH*
1-Phenol-2-sulfuric acid, formaldehyde condensate	Allied	Buffalo, NY
	Diamond Shamrock	Cedartown, GA*
	Rohm and Haas	Philadelphia, PA
Phenyl ether	Dow	Midland, MI
	Fritzsche	Clifton, NJ*
	Monsanto	Chocolate Bayou, TX
Phthalic anhydride	Allied	Buffalo, NY* Chicago, IL* El Segundo, CA Frankford, PA* Ironton, OH*
	BASF Wyandotte	Kearny, NJ
	Chevron	Perth Amboy, NJ* Richmond, CA
	Commonwealth Oil	Penuelas, PR*
	Conoco	Hebronville, MA*
	Exxon	Baton Rouge, LA
	W. R. Grace	Fords, NJ*
	Hooker	Arecibo, PR
	Koppers	Bridgeville, PA Chicago, IL* Cicero, IL
	Monsanto	Bridgeport, NJ Chocolate Bayou, TX* St. Louis, MO* Texas City, TX

(continued)

TABLE A3. (continued)

Chemical	Producer	Location
	Reichhold	Azusa, CA*
		Elizabeth, NJ*
		Morris, IL*
	Sherwin Williams	Chicago, IL*
Phthalic anhydride (continued)	Stand. Oil Co. Cal. (see Chevron)	
	Stepan Chem.	Elwood, IL
		Millsdale, IL*
	Union Carbide	Institute, WV*
		South Charleston, SC*
	U.S. Steel	Neville Island, PA
	Witco Chem.	Chicago, IL*
		Perth Amboy, NJ*
Picric acid	Allied	Buffalo, NY*
	du Pont	Deepwater, NJ*
	Hummel Chem.	South Plainfield, NJ*
	Martin Marietta	Sodyeco, NC
Sodium picrate	Hummel Chem.	South Plainfield, NJ
	Martin Marietta	Sodyeco, NC*
	Northrop	Asheville, NC
Tetrabromophthalic anhydride	Velsicol	St. Louis, MI
1,2,4,5-Tetrachlorobenzene	Dover	Dover, OH*
	Dow	Midland, MI
	Hooker	Niagara Falls, NY*
	Solvent Chem.	Malden, MA*
	Standard Chlorine	Delaware City, DE
Tetrachlorophthalic anhydride	Hooker	Niagara Falls, NY
	Monsanto**	Bridgeport, NJ
Tetrafluoro-*m*-phenylenediamine	Whittaker	San Diego, CA*
Tribromobenzene	Velsicol	St. Louis, MI*
	Northrop	Asheville, NC
1,2,4-Trichlorobenzene	Chris Craft	Newark, NJ*
	Dover	Dover, OH*
	Dow	Midland, MI
	Hooker	Niagara Falls, NY*
	Neville Chem.	Santa Fe Springs, CA*
	Sobin Chems.	Newark, NJ*
	Solvent Chem.	Malden, MA*
	Standard Chlorine	Delaware City, DE
		Kearny, NJ*
	Sun Chem.	Chester, SC*
2,4,6-Trinitroresorcinol	Northrop	Asheville, NC
	Olin	East Alton, IL

*No longer produced at this location.

**Possibly two plants.

TABLE A4. ALPHABETICAL LIST OF ORGANIC CHEMICAL PRODUCERS

Producer	Location	Chemical (class)
Aceto Chem. Co., Inc. 126-02 Northern Blvd. Flushing, NY 11368 Arsynco, Inc. Subsid.	Carlstadt, NJ	3,5-Dichlorosalicylic acid (II)
Alberta Gas Chems., Inc. Address not available	Duluth, MN	Fumaric acid (III)
Aldrich Chem. Co., Inc. 940 West St. Paul Av. Milwaukee, WI 53233	Milwaukee, WI	2,4-Dichlorophenol (I)* 2,6-Dichlorophenol (I) 3,4-Dichlorophenol
Allied Chem. Corp. Columbian Rd. and Park Av. Morristown, NJ 07960	Buffalo, NY	3-Amino-5-chloro-2-hydroxybenzenesulfonic acid (III)* Fumaric acid (III)* Maleic acid (III)* 1-Phenol-2-sulfonic acid, formaldehyde condensate (III)* Phthalic anhydride (III)* Picric acid (III)*
	Chicago, IL	Phthalic anhydride (III)*
	El Segundo, CA	Phthalic anhydride (III)
	Frankford, PA	Phthalic anhydride (III)*
	Ironton, OH	Phthalic anhydride (III)*
	Marcus Hook, PA	Maleic acid (III)
	Moundsville, WV	Fumaric acid (III)* Maleic acid (III)* Maleic anhydride (III)*
	Syracuse, NY	*o*-Dichlorobenzene (III)*
American Aniline Products, Inc. 25 McLean Blvd. P.O. Box 3063 Paterson, NJ 07509 Owned by Pepsi, Inc. 52% and Kopper Co., Inc., 48%	Lock Haven, PA	*o*-Anisidine (III)*
American Color and Chem. Corp. 11400 Westinghouse Blvd. P.O. Box 1688 Charlotte, NC 28201	Lock Haven, PA	*o*-Anisidine (III) 4-Chlororesorcinol (II)
Amoco Chems. Corp. 200 E. Randolph Dr. Chicago, IL 60601 Affiliate of Standard Oil Co., Indiana	Joliet, IL	Maleic anhydride (III)

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Arsynco	See Aceto	
Ashland Oil, Inc. 1409 Winchester Av. P.O. Box 391 Ashland, KY 41101	Neal, WV	Maleic anhydride (III)
BASF Wyandotte Corp. 100 Cherry Hill Road Parisppany, NJ 07054	Kearny, NJ	Phthalic anhydride (III)
Blue Spruce Co. 1390 Valley Road Stirling, NJ 07980	Bound Brook, NJ	3,4-Dichloroaniline (III) 1,2-Dichloro-4-nitrobenzene (III)
	Edison, NJ	3,4-Dichloroaniline (III)* 1,2-Dichloro-4-nitrophenol (III)*
Chemical Insecticide Corp. 30 Whitman Av. Metuchen, NJ 08840 No current address	Metuchen, NJ	3,4-Dichloroaniline (III)* 1,2-Dichloro-4-nitrobenzene (III)*
Chemical Products Corp. 48 Atlanta Road Cartersville, GA 30120	Cartersville, GA	*o*-Dichlorobenzene (III)*
Chevron Chem. Co. 575 Market Street San Francisco, CA 94105 Subsid. Standard Oil Co. of California	Richmond, CA	Maleic anhydride (III)* Phthalic anhydride (III)
	Perth Amboy, NJ	Phthalic anhydride (III)*
Chris Craft Industry, Inc. 600 Madison Av New York, NY See Montrose Chem.	Newark, NJ	1,2,4-Trichlorobenzene (III)*
Commonwealth Oil Refining Co., Inc. 425 Park Av. New York, NY 10017	Penuelas, PR	Phthalic anhydride (III)*
Continental Oil Co. (Conoco) Petrochemicals Dept. Saddle Brook, NJ 07662	Hebronville, MA	Phthalic anhydride (III)*
Crompton and Knowles Corp. 345 Park Av. New York, NY 10022	Fair Lawn, NJ	Benzaldehyde (III)

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Diamond Shamrock Corp. 1100 Superior Av. Cleveland, OH 44114	Cedartown, GA	1-Phenol-2-sulfonic acid, formaldehyde condensate (III)*
	Newark, NJ	2,4-Dichlorophenol (I)*
Dover Chem. Corp. West 15th St. Dover, OH 44622 Affiliate of ICC Industries, Inc.	Dover, OH	*o*-Dichlorobenzene (III)* Hexachlorobenzene (III)* 1,2,4,5-Tetrachlorobenzene (III)* Tetrachlorobisphenol-A (II)* 1,2,4-Trichlorobenzene (III)*
Dow Chem. U.S.A. 2020 Dow Center Midland, MI	Kalama, WA Midland, MI	Benzaldehyde (III)* *o*-Chlorophenol (II) 2-Chloro-4-phenylphenol (II) 2,4-Dibromophenol (I) *o*-Dichlorobenzene (III) 2,4-Dichlorophenol (I) Pentabromochlorocyclohexane (III) Phenol (III)*, ** Phenyl ether (III) Tetrabromobisphenol-A (II) 1,2,4,5-Tetrachlorobenzene (III) 2,4,6-Tribromophenol (I)* 1,2,4-Trichlorobenzene (III)
E.I. du Pont de Nemours and Co., Inc. 1007 Market St. Wilmington, DE 19898	Deepwater, NJ	*o*-Anisidine (III) 4-Chloro-2-nitrophenol (III)* 3,4-Dichloroaniline (III) *o*-Dichlorobenzene (III)* 2-Nitro-*p*-cresol (III)* *o*-Nitrophenol (III)* *o*-Nitroanisole (III)
Eastern Chem. Corp. Now Eastern Chem. Div. of Guardian Chem. Corp.	Pequannock, NJ	Chlorohydroquinone (II)* 2,4,6-Tribromophenol (I)*
Eastman Kodak Co. 343 State St. Rochester, NY 14650	Rochester, NY	*o*-Bromophenol (II) Chlorohydroquinone (II) 2,5-Dihydroxybenzenesulfonic acid (III)* 2,5-Dinitrosalicylic acid (III) Maleic acid (III)*
Exxon Corp. 1251 Av. of the Americas New York, NY 10020	Baton Rouge, LA	Phthalic anhydride (III)

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Fairmount Chem. Co., Inc. 117 Blanchard St. Newark, NJ 07105	Newark, NJ	2-Chloro-1,4-diethoxy-5-nitrobenzene (II)
Fritzsche Dodge and Olcott, Inc. 76 Ninth Av. New York, NY 10011	Clifton, NJ	Benzaldehyde (III)* Phenyl ether (III)*
GAF Corp. 140 West 51st St. New York, NY 10020	Rensselaer, NY	2-Chloro-1,4-diethoxy-5-nitrobenzene (II) 5-Chloro-2,4-dimethoxy-aniline (II) 4-Chlororesorcinol (II)
W. R. Grace and Co. 7 Hanover Square New York, NY 10005	Fords, NJ	Phthalic anhydride (III)*
Great Lakes Chem. Corp. Hwy. 52, Northwest West Lafayette, IN 47906	El Dorado, AR	Decabromophenoxy-benzene (I) Tetrabromobisphenol-A (II)
Guardian Chem. Corp. 230 Marcus Blvd. Hauppauge, NY 11787	Hauppauge, NY	Chlorohydroquinone (II)* 2,4,6-Tribromophenol (I)
Hexcel Corp. 11711 Dublin Blvd. Dublin, CA 94566	Sayerville, NJ	Pentabromoethylbenzene (III)
Hooker Chem. Corp. 1900 St. James Place Houston, TX 77027 Subsid. Occidental Petroluem Corp.	Arecibo, PR	Fumaric acid (III) Phthalic anhydride (III)
	Niagara Falls, NY	*o*-Dichlorobenzene (III)* Tetrachlorophthalic anhydride (III)* 1,2,4,5-Tetrachlorobenzene (III)* 1,2,4-Trichlorobenzene (III)*
	North Tonawanda, NY	Phenol (III)*, **
	South Shore, KY	Phenol (III)*, **
Hummel Chem. Co., Inc. P.O. Box 250 South Plainfield, NJ 07080	Newark, NJ	2,4-Dinitrophenoxyethanol (III)* 3,5-Dinitrosalicylic acid (III)* Hexachlorobenzene (III)* Picric acid (III)*
	South Plainfield, NJ	2,4-Dinitrophenoxyethanol (III) 3,5-Dinitrosalicylic acid (III)* Hexachlorobenzene (III)* Picric acid (III)* Sodium picrate (III)

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
ICC Industries See Solvent Chem.		
Inmont Corp. 1133 Av. of the Americas New York, NY 10036 Subsid. of Carrier Corp.	Carlstadt, NJ NOTE: Carlstadt Plant listed under Interchemical Corp. which was acquired by Inmont Corp.	3,5-Dichlorosalicylic acid (III)*
International Mineral and Chem. Corp. IMC Plaza Libertyville, IL 60048	Newark, NJ	1,2,4-Trichlorobenzene (III)*
Kalama Chemc, Inc. The Bank of California Center Suite 1110 Kalama, WA	Kalama, WA	Benzaldehyde (III)
Kopper Co., Inc. Koppers Bldg. Pittsburgh, PA 15219	Bridgeville, PA	Maleic anhydride (III) Phthalic anhydride (III)
	Chicago, IL	Phthalic anhydride (III)*
	Cicero, IL	Maleic anhydride (III)* Phthalic anhydride (III)
Martin Marietta Corp. 6801 Rockledge Dr. Bethesda, MD 20034	Sodyeco, NC	2,6-Dibromo-4-nitrophenol (II)* 3,4-Dichloroaniline (III)* 1,2-Dichloroaniline (III)* 1,2-Dichloro-4-nitrobenzene (III)* 2,4-Dinitrophenol (III) Picric acid (III) Sodium picrate (III)*
Maumee Chem. Co. Presumed to be acquired by Sherwin Williams Address not available	St. Bernard, OH	2,6-Dibromo-4-nitrophenol (II)* 4-Chloro-2-nitrophenol (III)*
Mobay Chem. Co. Penn Lincoln Pkwy. West Pittsburgh, PA 15205	New Martinsville, WV	3,4-Dichlorophenylisocyanate (III) 2,4-Dinitrophenol (III)
Monroe Chem. Co. Saville Av. at 4th St. Eddystone, PA Subsid. of Kalama Chem., Inc. (see Kalama)	Eddystone, PA	Benzaldehyde (III)

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Monsanto Co. 800 North Lindbergh Blvd. St. Louis, MO 63166	Bridgeport, NJ	Phthalic anhydride (III) Tetrachlorophthalic anhydride (III)
	Chocolate Bayou, TX	Phenyl ether (III) Phthalic anhydride (III)*
	Luling LA	3,4-Dichloroaniline (III)
Monsanto (continued)	Sauget, IL	*o*-Chlorophenol (II) 3,4-Dichloroaniline (III)* *o*-Dichlorobenzene (III) 1,2-Dichlor-4-nitrobenzene (III)* 2,4-Dichlorophenol (I) *o*-Nitroanisole (III)* *o*-Nitrophenol (III)
	St. Louis, MO	*o*-Anisidine (III)* Fumaric acid (III) Maleic anhydride (III) *o*-Nitroanisole (III) *o*-Phenetidine (III)* Phthalic anhydride (III)*
	Texas City, TX	Phthalic anhydride (III)*
Montrose Chem. Corp. of California 2401 Morris Av. P.O. Box E Union, NJ 07083 Jointly owned by Chris Craft Industries, Inc. and Stauffer Chem. Co.	Henderson, NV	*o*-Dichlorobenzene (III)
Morton Chem. Co., Div. Morton-Norwich Products, Inc. 110 North Wacker Dr. Chicago, IL 60606	Ringwood, IL	3,5-Diiodosalicylic acid (II)*
Nease Chem. Co., Inc. P.O. Box 221 State College, PA 16801	State College, PA	2,5-Dihydroxybenzenesulfonic acid (III)* 2,5-Dihydroxybenzenesulfonic acid, potassium salt (III)*
Neville Chem. Co. Neville Island Pittsburgh, PA 15225	Santa Fe Springs, CA	*o*-Dichlorobenzene (III)* 1,2,4-Trichlorobenzene (III)*
Northrop Corp. 1800 Century Park, East Los Angeles, CA 90067	Asheville, NC	Sodium picrate (III) Tribromobenzene (III) 2,4,6-Trinitroresorcinol (III)

(continued)

TABLE A4. (continued)

Producer	**Location**	**Chemical (class)**
Northwest Industries (See Velsicol) G 300 Sears Tower Chicago, IL 60606		
Nyanza, Inc. 200 Sutton St. North Andover, MA 01721	Ashland, MA	3-Amino-5-chloro-2-hydroxybenzenesulfonic (III) 2-Amino-4-chloro-6-nitrophenol (III)
Occidental Petroleum Corp. (See Hooker) 10889 Wilshire Blvd. Suite 1500 Los Angeles, CA 90024		
Olin Corp. 120 Long Ridge Rd. Stamford, CT 06904	East Alton, IL McIntosh, AL Rochester, NY	2,4,6-Trinitroresorcinol (III)* *o*-Dichlorobenzene (III)* *o*-Bromofluorobenzene (III) *o*-Chlorofluorobenzene (III) 3-Chloro-4-fluoronitrobenzene (III) 2-Chloro-4-fluorophenol (I) 3-Chloro-4-fluorophenol (III) 2,4-Dibromofluorobenzene (III) 3,4-Difluoroaniline (III) *o*-Difluorobenzene (III) *o*-Fluoroanisole (II) Pentachloroaniline (III)
Ott Chem. Co. See Story Chem.		
PCR, Inc. P.O. Box 1466 Gainesville, FL 32602	Gainesville, FL	Hexafluorobenzene (III)
Petro-Tex Chem. Corp. 8600 Park Place Houston, TX 77017 Jointly owned by FMC Corp. and Tenneco, Inc.	Houston, TX	Fumaric acid (III)* Maleic anhydride (III)*
Pfister Chem., Inc. Linden Av. Ridgefield, NJ 07657	Newark, NJ	2-Chloro-1,4-diethoxy-5-nitrobenzene (II)* 5-Chloro-2,4-dimethoxyaniline (II)*
	Ridgefield, NJ	5-Chloro-2,4-dimethoxyaniline (II)

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Pfizer, Inc. 235 East 42nd St. New York, NY 10017	Terre Haute, IN	Fumaric acid (III)
Plastifax, Inc. Indust. Seaway Blvd. P.O. Box 1056 Gulfport, MS 39501	Gulf Port, MS	1,2-Dichloro-4-nitrobenzene (III)
PPG Industries, Inc. One Gateway Center Pittsburgh, PA 15222	Natrium, WV	*o*-Dichlorobenzene (III)
Reichhold Chems., Inc. RCI Bldg. White Plains, NY 10603	Azusa, CA	Phthalic anhydride (III)*
	Elizabeth, NJ	Maleic anhydride (III) Phthalic anhydride (III)*
	Morris, IL	Fumaric acid (III)* Maleic anhydride (III) Phthalic anhydride (III)*
Rhodia, Inc. 600 Madison Av. New York, NY 10022	Freeport, TX	2,4-Dichlorophenol (I)
F. Ritter and Co. 4001 Goodwin Av. Los Angeles, CA 90039	Los Angeles, CA	Benzaldehyde (III)*
Rohm and Haas Co. Independence Mall West Philadelphia, PA 19105	Philadelphia, PA	1-Phenol-2-sulfonic acid, formaldehyde condensate (III)
R.S.A. Corp. 690 Saw Mill River Road Ardsley, NY 10502	Ardsley, NY	Bromophenetole (II) *o*-Bromophenol (II) 2,6-Diiodo-4-nitrophenol (II) 3,5-Diiodosalicylic acid (II)* Pentabromophenol (I)* 2,4,6-Tribromophenol (I)*
Salsbury Labs 2000 Rockford Road Charles City, IA	Charles City, IA	3,5-Dinitrosalicyclic acid (III)
Sherwin Williams Co. 101 Prospect Av. Cleveland, OH 44101	Chicago, IL	2-Nitro-*p*-cresol (III) Phthalic anhydride (III)*
	St. Bernard, OH	2,6-Dibromo-4-nitrophenol (II)* 4-Chloro-2-nitrophenol (III)*
Sobin Chems. Inc. See International Minerals and Chemicals Corp.		

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Solvent Chem. Co., Inc. 720 Fifth Av. New York, NY 10011 Affiliate of ICC Industries	Malden, MA	*o*-Dichlorobenzene (III)* 1,2,4,5-Tetrachlorobenzene (III)* 1,2,4-Trichlorobenzene (III)*
	Niagara Falls, NY	*o*-Dichlorobenzene (III)
Specialty Organics, Inc. 5263 North Fourth St. Irwindale, CA 91706	Irwindale, CA	2,3-Dichlorophenol (I) 2,6-Dichlorophenol (I) *o*-Dichlorobenzene (III)
Standard Chlorine Chem. Co., Inc. 1035 Belleville Turnpike Kearny, NJ 07032	Delaware City, DE	*o*-Dichlorobenzene (III) 1,2,4,5-Tetrachlorobenzene (III) 1,2,4-Trichlorobenzene (III)
	Kearny, NJ	*o*-Dichlorobenzene (III) 1,2,4-Trichlorobenzene (III)*
Standard Oil Co. (California) (See Chevron) 575 Market St. San Francisco, CA 94105		
Standard Oil Co. (Indiana) (See Amoco) 910 South Michigan Av. Chicago, IL 60605		
Standard Oil Co. (New Jersey) (See Exxon)		
Stauffer Chem. Co. Westport, CT 06880	Edison, NJ	Benzaldehyde (III)*
	Nixon, NJ	Benzaldehyde (III)*
	Louisville, KY	Hexachlorobenzene (III)*
Stepan Chem. Co. Edens and Winnetka Rd. Northfield, IL 60093	Elwood, IL	Phthalic anhydride (III)
	Fieldsboro, NJ	Fumaric acid (III)*
	Millsdale, IL	Phthalic anhydride (III)*
Stering Drug, Inc. 90 Park Av. New York, NY 10016	New York, NY	1,2-Dihydroxy-3,5-disulfonic acid, disodium salt (III)*
Story Chem. Corp. 500 Agard Rd. Muskegan, MI 49445 Ott Chem. Co., Div.	Muskegan, MI	3,4-Dichlorophenylisocyanate (III)*
Sun Chem. Corp. Box 70 Chester, SC 29706	Chester, SC	1,2,4-Trichlorobenzene (III)*

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Tenneco Chems. Co. Park 80 Plaza, West Saddle Brook, NJ 07662 Part of Tenneco, Inc.	Fords, NJ	Benzaldehyde (III)* 3,4-Dichlorobenzaldehyde (III) 3,4-Dichlorobenzotrichloride (III) 3,4-Dichlorobenzotrifluoride (III)* Maleic anhydride (III)
	Garfield, NJ	Fumaric acid (III) Benzaldehyde (III)
Toms River Chem. Corp. P.O. Box 71 Toms River, NJ 08753 Owned by Ciba-Geigy 80% and Sandoz AZ 20%	Toms River, NJ	3-Amino-5-chloro-2-hydroxybenzenesulfonic acid (III)
Transvaal, Inc. Marshall Road P.O. Box 69 Jacksonville, AR 72076 (Subsid. of Vertac)	Jacksonville, AR	2,4-Dichlorophenol (I)
Union Carbide Corp. 270 Park Av. New York, NY 10017	Marietta, OH	Phenol (III)*, **
UOP, Inc. Ten UOP Plaza Algonquin and Mt. Prospect Roads Des Plaines, IL 60016	East Rutherford, NJ	Benzaldehyde (III)
U.S. Steel Corp. Sixth and Grant Pittsburgh, PA 15230	Neville Island, PA	Fumaric acid (III) Maleic anhydride (III) Phthalic anhydride (III)
Velsicol Chem. Corp. 341 East Ohio St. Chicago, IL 60611 Subsid. of Northwest Industries, Inc.	Beaumont, TX	4-Bromo-2,5-dichlorophenol (I) 2,5-Dichlorophenol (I)
	Chattanooga, TN	Benzaldehyde (III)*
	St. Louis, MI	Hexabromobenzene (III)* Pentabromophenol (I)* Tetrabromobisphenol—A (II) Tetrabromophthalic anhydride (III) Tribromobenzene (III)* 2,4,6-Tribromophenol (I)*

(continued)

TABLE A4. (continued)

Producer	Location	Chemical (class)
Vertac, Inc. (See Transvaal) 2414 Clark Tower Memphis, TN 38137		
White Chem. Corp. P.O. Box 278 Bayonne, NJ 07002	Bayonne, NJ	2,4-Dibromophenol (I) Pentabromophenol (I) Pentabromotoluene (III) 2,4,6-Tribromophenol (I)
Whittaker Corp. 10880 Wilshire Blvd. Los Angeles, CA 90024	San Diego, CA	Hexafluorobenzene (III)* Pentafluoroaniline (III)* Chloropentafluorobenzene (III)* Tetrafluoro-*m*-phenylenediamine (III)*
Witco Chem. Corp. 277 Park Av. New York, NY 10017	Chicago, IL	Phthalic anhydride (III)*
	Perth Amboy, NJ	Phthalic anhydride (III)*

*No longer produced at this location.

**From chlorobenzene.

TABLE A5. FORMER LOCATIONS OF ORGANIC CHEMICAL PRODUCTION

Producer	Location	Chemical (class)
Aldrich	Milwaukee, WI	2,4-Dichlorophenol (I)
Allied	Buffalo, NY	3-Amino-5-chloro-2-hydroxybenzenesulfonic acid (III)
		Fumaric acid (III)
		Maleic acid (III)
		1-Phenol-2-sulfonic acid, formaldehyde condensate (III)
		Phthalic anhydride (III)
	Chicago, IL	Phthalic anhydride (III)
Frankford, PA		Phthalic anhydride (III)
	Ironton, OH	Phthalic anhydride (III)
	Moundsville, WV	Fumaric acid (III)
		Maleic acid (III)
		Maleic anhydride (III)
	Syracuse, NY	*o*-Dichlorobenzene (III)
Am. Aniline	Lock Haven, PA	*o*-Anisidine (III)
Blue Spruce	Edison, NJ	3,4-Dichloroaniline (III)
		1,2-Dichloro-4-nitrobenzene (III)
Chem. Insecticide	Metuchen, NJ	3,4-Dichloroaniline (III)
		1,2-Dichloro-4-nitrobenzene (III)
Chem. Products	Cartersville, GA	*o*-Dichlorobenzene (III)
Chevron	Richmond, CA	Maleic anhydride (III)
	Perth Amboy, NJ	Phthalic anhydride (III)
Chris Craft	Newark, NJ	1,2,4-Trichlorobenzene (III)
Commonwealth Oil	Penuelas, PR	Phthalic anhydride (III)
Conoco	Hebronville, MA	Phthalic anhydride (III)
Dover	Dover, OH	*o*-Dichlorobenzene (III)
		Hexachlorobenzene (III)
		1,2,4,5-Tetrachlorobenzene (III)
		Tetrachlorobisphenol-A (II)
		Tetrachlorobisphenol-A (II)
		1,2,4-Trichlorobenzene (III)
Diamond Shamrock	Cedartown, GA	1-Phenol-2-sulfonic acid, formaldehyde condensate (III)
Dow	Midland, MI	Phenol (III)*
		2,4,6-Tribromophenol (I)
	Kalama, WA	Benzaldehyde (III)

(continued)

TABLE A5. (continued)

Producer	Location	Chemical (class
du Pont	Deepwater, NJ	4-Chloro-2-nitrophenol (III) *o*-Dichlorobenzene (III) 2-Nitro-*p*-cresol (III) *o*-Nitrophenol (III)
Eastern Chem. (Currently Eastern Chem. Div. of Guardian)	Pequannock, NJ	Chlorohydroquinone (II) 2,4,6-Tribromophenol (I)
Eastman Kodak	Rochester, NY	2,5-Dihydroxybenzenesulfonic acid (III) Maleic acid (III)
Fritzsche	Clifton, NJ	Benzaldehyde (III) Phenyl ether (III)
W. R. Grace	Fords, NJ	Phthalic anhydride (III)
Guardian	Hauppauge, NY	Chlorohydroquinone (II)
	Pequannock, NJ	Chlorohydroquinone (II) 2,4,6-Tribromophenol (I)
Hooker	Niagara Falls, NY	*o*-Dichlorobenzene (III) Tetrachlorophthalic anhydride (III) 1,2,4,5-Tetrachlorobenzene (III) 1,2,4-Trichlorobenzene (III)
	North Tonawanda, NY	Phenol (III)*
	South Shore, KY	Phenol (III)*
Hummel Chem.	Newark, NJ	2,4-Dinitrophenoxyethanol (III) 3,5-Dinitrosalicylic acid (III) Hexachlorobenzene (III) Picric acid (III)
	South Plainfield, NJ	3,5-Dinitrosalicylic acid (III) Hexachlorobenzene (III) Picric acid (III)
Inmont (formerly Interchemical Corp.)	Carlstadt, NJ	3,5-Dichlorosalicylic acid (III)
Koppers	Chicago, IL	Phthalic anhydride (III)
	Cicero, IL	Maleic anhydride (III)
Martin Marietta	Sodyeco, NC	2,6-Dibromo-4-nitrophenol (II) 3,4-Dichloroaniline (III) 1,2-Dichloro-4-nitrobenzene (III) Sodium picrate (III)

(continued)

TABLE A5. (continued)

Producer	Location	Chemical (class)
Monsanto	Chocolate Bayou, TX	Phthalic anhydride (III)
	Sauget, IL	3,4-Dichloroaniline (III) 1,2-Dichloro-4-nitrobenzene (III) *o*-Nitroanisole (III)
	St. Louis, MO	*o*-Anisidine (III) *o*-Phenetidine (III) Phthalic anhydride (III)
Morton Chem.	Ringwood, IL	3,5-Diiodosalicylic acid (II)
Nease Chem.	State College, PA	2,5-Dihydroxybenzenesulfonic acid (III) 2,5-Dihydroxybenzenesulfonic acid and potassium salt (III)
Neville Chem.	Santa Fe Springs, CA	*o*-Dichlorobenzene (III) 1,2,4-Trichlorobenzene (III)
Olin	East Alton, IL	2,4,6-Trinitroresorcinol (III)
	McIntosh, AL	*o*-Dichlorobenzene (III)
Petro-Tex	Houston, TX	Fumaric acid (III) Maleic anhydride (III)
Pfister	Newark, NJ	2-Chloro-1,4-diethoxy-5-nitrobenzene (II) 5-Chloro-2,4-dimethoxyaniline (II)
Reichhold	Azusa, CA	Phthalic anhydride (III)
	Elizabeth, NJ	Phthalic anhydride (III)
	Morris, IL	Fumaric acid (III) Phthalic anhydride (III)
F. Ritter	Los Angeles, CA	Benzaldehyde (III)
R.S.A.	Ardsley, NY	3,5-Diiodosalicylic acid (II) Pentabromophenol (I) 2,4,6-Tribromophenol (I)
Sherwin Williams	St. Bernard, OH	2,6-Dibromo-4-nitrophenol (II) 4-Chloro-2-nitrophenol (III) Phthalic anhydride (III)
Sobin Chems. (currently International Minerals and Chems. Corp.)	Newark, NJ	1,2,4-Trichlorobenzene (III)
Solvent Chem.	Malden, MA	*o*-Dichlorobenzene (III) 1,2,4,5-Tetrachlorobenzene (III) 1,2,4-Trichlorobenzene (III)

(continued)

TABLE A5. (continued)

Producer	Location	Chemical (class)
Standard Chlorine	Kearny, NJ	1,2,4-Trichlorobenzene (III)
Stauffer	Edison, NJ	Benzaldehyde (III)
	Louisville, KY	Hexachlorobenzene (III)
	Nixon, NJ	Benzaldehyde (III)
Stepan Chem.	Fieldsboro, NJ	Fumaric acid (III)
	Millsdale, IL	Phthalic anhydride (III)
Sterling Drug	New York, NY	1,2-Dihydroxy-3,5-disulfonic acid, disodium salt (III)
Story Chem.	Muskegan, MI	3,4-Dichlorophenylisocyanate (III)
Sun Chem.	Chester, SC	1,2,4-Trichlorobenzene (III)
Tenneco	Fords, NJ	3,4-Dichlorobenzotrifluoride (III)
Union Carbide	Marietta, OH	Phenol (III)*
Velsicol	Chattanooga, TN	Benzaldehyde (III)
	St. Louis, MI	Hexabromobenzene (III)
		Pentabromophenol (I)
		Tribromobenzene (III)
		2,4,6-Tribromophenol (I)
Whittaker	San Diego, CA	Hexafluorobenzene (III)
		Pentafluoroaniline (III)
		Chloropentafluorobenzene (III)
		Tetrafluoro-*m*-phenylenediamine (III)
Witco	Chicago, IL	Phthalic anhydride (III)
	Perth Amboy, NJ	Phthalic anhydride (III)

*From chlorobenzene.

TABLE A6. PRODUCERS OF PESTICIDE CHEMICALS, CLASSES I AND II

Chemical	Producer	Location
Class I		
Bifenox	Mobil	Mt. Pleasant, TN
Chloranil	Arapahoe	Boulder, CO*
	Uniroyal	Naugatuck, CT*
2,4-D and esters and salts	Amchem	Ambler, PA
		Fremont, CA
		St. Joseph, MO
	Chemical Insecticide Corp.	Metuchen, NJ*
	Chempar	Portland, OR*
	Diamond Shamrock	Newark, NJ*
	Dow	Midland, MI
	Fallek-Lankro	Tuscaloosa, AL
	Guth Chem.	Hillside, IL*
	Imperial	Shenandoah, IA
	Miller Chem.	Whiteford, MD*
	Monsanto	Sauget, IL*
	PBI-Gordon	Kansas City, KS
	Rhodia	N. Kansas City, MO*
		Portland, OR
		St. Joseph, MO
		St. Paul, MN*
	Riverdale	Chicago Hgts., IL
	Thompson Chem.	St. Louis, MO*
	Thompson-Hayward	Kansas City, KS
	Transvaal	Jacksonville, AR
	Woodbury	Orlando, FL*
2,4-DB and salts	Amchem	Ambler, PA
	Rhodia	N. Kansas City, MO*
		Portland, OR
		St. Joseph, MO
		St. Paul, MN*
Dicamba	Velsicol	Beaumont, TX
		Chattanooga, TN*
Dicapthon	American Cyanamid	Warners, NJ*
Dichlofenthion	Mobile	Charleston, SC*
		Mt. Pleasant, TN*
Dimethylamine salt of dicamba	PBI-Gordon	Kansas City, KS
Disul sodium (sesone)	Amchem	Ambler, PA*
		Fremont, CA*
		Linden, NJ*
		St. Joseph, MO*

(continued)

TABLE A6. (continued)

Chemical	Producer	Location
	GAF	Linden, NJ*
	Union Carbide	Institute and South Charleston, WV*
2,4-DP	Rhodia	Portland, OR
	Transvaal	Jacksonville, AR
Erbon	Dow	Midland, MI*
Hexachlorophene	Givaudan	Clifton, NJ
Isobac 20	Givaudan	Clifton, NJ
Nitrofen	Rohm and Haas	Philadelphia, PA
Pentachlorophenol (PCP) and and salts	Dow	Midland, MI
	Merck	Hawthorne, NJ*
	Monsanto	Sauget, IL
	Reichhold	Tacoma, WA
	Sonford Chemical	Port Neches, TX*
	Vulcan Materials	Wichita, KS
Ronnel	Dow	Midland, MI
Silvex and esters and salts	Dow	Midland, MI
	Guth Chemical	Hillside, IL*
	Millmaster Onyx	Berkeley Hgts., NJ*
	Riverdale	Chicago Hgts., IL
	Thompson-Hayward	Kansas City, KS
	Transvaal	Jacksonville, AR
2,4,5-T and esters and salts	Amchem	Ambler, PA
		Fremont, CA
		St. Joseph, MO
	Chemical Insecticide Corp.	Metuchen, NJ*
	Chempar	Portland, OR*
2,4,5-T and esters and salts (continued)	Diamond Shamrock	Newark, NJ*
	Dow	Midland, MI
	Guth Chemical	Hillside, IL*
	Hercules	Brunswick, GA*
	Millmaster Onyx	Berkeley Hgts., NJ*
	PBI-Gordon	Kansas City, KS
	Riverdale	Chicago Hgts., IL
	Thompson Chemical	St. Louis, MO*
	Thompson-Hayward	Kansas City, KS
	Transvaal	Jacksonville, AR
2,3,4,6-Tetrachlorophenol	Dow	Midland, MI
	Sonford	Port Neches, TX*

(continued)

TABLE A6. (continued)

Chemical	Producer	Location
2,4,5-Trichlorophenol and salts	Chemical Insecticide Corp.	Metuchen, NJ*
	Diamond Shamrock	Newark, NJ*
	Dow	Midland, MI
	GAF	Linden, NJ*
	Hercules	Brunswick, GA*
	Hooker	Niagara Falls, NY*
	N. Eastern Pharmacy	Verona, MO*
	Transvaal	Jacksonville, AR
2,4,6-Trichlorophenol	Dow	Midland, MI
Class II		
o-Benzyl-*p*-chlorophenol	Monsanto	Sauget, IL
	Reichhold	Tacoma, WA
Bromoxynil and esters	Amchem	Ambler, PA
	Rhodia	Portland, OR
		St. Joseph, MO
Carbophenothion	Stauffer	Cold Creek, AL*
		Henderson, NV
Chlorothalonil	Diamond Shamrock	Greens Bayou, TX
DCPA	Diamond Shamrock	Greens Bayou, TX
Dichlone	Aceto	Flushing, NY*
	FMC	Middleport, NY
	Uniroyal	Naugatuck, CT*
Dinitrobutylphenol, ammonium salt	Dow	Midland, MI
4,6-Dinitro-*o*-cresol and sodium salt	Blue Spruce	Bound Brook, NJ
Ioxynil	Amchem	Fremont, CA*
	Rhodia	Portland, OR*
Lindane	Hooker	Niagara Falls, NY
	Prentiss	Newark, NJ
MCPA and derivatives	Diamond Shamrock	Newark, NJ*
	Dow	Midland, MI
	Fallek-Lankro	Tuscaloosa, AL
	Guth Chemical	Hillside, IL*
	Monsanto	Nitro, WV*
	Rhodia	Portland, OR

(continued)

TABLE A6. (continued)

Chemical	Producer	Location
MCPB	Amchem	Ambler, PA
		Fremont, CA
		St. Joseph, MO
	Dow	Midland, MI*
	Monsanto	Sauget, IL*
	Rhodia	Portland, OR
		St. Joseph, MO
Mecoprop	Cleary	Somerset, NJ
	Fallek-Lankro	Tuscaloosa, AL
	Morton Chem.	Ringwood, IL*
	PBI-Gordon	Kansas City, KS
	Rhodia	Portland, OR
		St. Joseph, MO
Parathion	American Cyanamid	Warners, NJ*
	American Potash	Hamilton, MS*
		Los Angeles, CA*
	Monsanto	Anniston, AL
	Stauffer	Mt. Pleasant, TN*
	Velsicol	Bayport, TX*
PCNB	Monsanto	Sauget, IL*
	Olin	Leland, MS
		McIntosh, AL
		Rochester, NY*
Pipecolinopropyl-3,4-dichlorobenzoate	Eli Lilly	Lafayette, IN
Piperalin	Eli Lilly	Indianapolis, IN*
		Lafayette, IN
Propanil	Blue Spruce	Bound Brook, NJ
	Eagle River	Helena, AR
	Monsanto	Luling, LA*
	Sobin Chemical	Newark, NJ
Tetradifon	FMC	Baltimore, MD*
2,3,6-Trichlorobenzoic acid	Amchem	Ambler, PA
		Fremont, CA
		St. Joseph, MO
	du Pont	Deepwater, NJ*
	Tenneco	Fords, NJ*
2,3,6-Trichlorophenyl acetic acid and sodium salt	Amchem	Ambler, PA
		Fremont, CA
		St. Joseph, MO
	Tenneco	Fords, NJ*
Triiodobenzoic acid	Amchem	Ambler, PA
	Mallinckrodt	Raleigh, NC*

*No longer produced at this location.

TABLE A7. ALPHABETICAL LIST OF PESTICIDE CHEMICAL PRODUCERS

Producer	Location	Chemical (class)
Aceto Chem. Co., Inc.	Flushing, NY	Dichlone (II)*
Alco Standard Corp. (see Miller Chem.)		
Amchem Products, Inc. Brookside Av. P.O. Box 33 Ambler, PA 19002 (Subsid. of Union Carbide)	Ambler, PA	2,4-D and esters and salts (I) 2,4-DB and salts (I) Disul sodium (I)* 2,4,5-T and esters and salts (I) Bromoxynil and esters (II) MCPB (II) 2,3,6-Trichlorobenzoic acid and salt (II) Triiodobenzoic acid (II)
	Fremont, CA	2,4-D and esters and salts (I) Disul sodium (I)* 2,4,5-T and esters and salts (I) Ioxynil (II)* MCPB (II)* 2,3,6-Trichlorophenyl acetic acid, sodium salt (II)
	Linden, NJ	Disul sodium (I)*
	St. Joseph, MO	2,4-D and esters and salts (I) Disul sodium (I)* 2,4,5-T and esters and salts (I) MCPB (II) 2,3,6-Trichlorobenzoic acid (II) 2,3,6-Trichlorophenyl acetic acid, sodium salt (II)
American Cyanamid Co. Berdan Av. Wayne, NJ 07470	Warners, NJ	Dicapthon (I)* Parathion (II)*
American Potash and Chem. Corp. Kerr-McGee Chem. Corp. Kerr-McGee Center Oklahoma City, OK 73125	Hamilton, MS	Parathion (II)*
	Los Angeles, CA	Parathion (II)*
Arapahoe Chem. Div. Syntex Corp. 3401 Hillview Av. Palo Alto, CA 94304	Boulder, CO	Chloranil (I)*
Blue Spruce Co. Stirling, NJ 07980	Bound Brook, NJ	4,6-Dinitro-*o*-cresol and sodium salt (II) Propanil (II)

(continued)

TABLE A7. (continued)

Producer	Location	Chemical (class)
Chemical Insecticide Corp. 30 Whitman Av. Metuchen, NJ 08840 (1971 address)	Metuchen, NJ	2,4-D and esters and salts (I)* 2,4,5-T and esters and salts (I)* 2,4,5-Trichlorophenol (I)*
Chempar Chem. Co., Inc. (address not available)	Portland, OR	2,4-D and esters and salts (I)* 2,4,5-T and esters and salts (I)*
W. A. Cleary 1049 Somerset St. Somerset, NJ 08873	Somerset, NJ	Mecoprop (II)
Diamond Shamrock Corp. 1100 Superior Av. Cleveland, OH 44114	Greens Bayou, TX	Chlorothalonil (II) DCPA (II)
	Newark, NJ	2,4-D and esters and salts (I)* 2,4,5-T and esters and salts (I)* 2,4,5-Trichlorophenol and salts (I)* MCPA (II)*
Dow Chemical U.S.A.	Midland, MI	2,4-D and esters and salts (I) Dinitrobutylphenol ammonium salt (II) Erbon (I)* MCPA and derivatives (II) MCPB (II)* Pentachlorophenol and salts (I) Ronnel (I) Silvex and esters and salts (I) 2,4,5-T and esters and salts (I) 2,4,5-Trichlorophenol (I) 2,4,6-Trichlorophenol (I)
E. I. du Pont de Nemours and Co., Inc. 1007 Market St. Wilmington, DE 19898	Deepwater, NJ	2,3,6-Trichlorobenzoic acid and salts (II)*
Eagle River Chemicals Co. Helena, AR 72342 (Subsid. of Vertac, Inc.)	Helena, AR	Propanil (II)
Eli Lilly and Co. 740 S. Alabama St. Indianapolis, IN 96206	Indianapolis, IN	Piperalin (II)*
	Lafayette, IN	Pipecolinopropyl-3,4-dichlorobenzoate (II) Piperalin (II)

(continued)

TABLE A7. (continued)

Producer	Location	Chemical (class)
FMC Corp. One Illinois Center 200 East Randolph Dr. Chicago, IL 60601	Baltimore, MD Middleport, NY	Tetradifon (II)* Dichlone (I)
Fallek-Lankro Corp. P.O. Box H Tuscaloosa, AL 35401 (Joint venture of Fallek Chem. Corp. and Lankro Chem. Group Ltd. [UK])	Tuscaloosa, AL	2,4-D and esters and salts (I) MCPA and derivatives (II) Mecoprop (II)
GAF Corp. 140 West 51st St. New York, NY 10020	Linden	Disul sodium (I)* 2,4,5-Trichlorophenol and salts (I)*
Givaudan Corp. 100 Delawanna Av. Clifton, NJ 07014 (Affiliate of L. Givaudan and Cie [Switz.])	Clifton, NJ	Hexachlorophene (I) Isobac 20 (I)
Guth Chemical Co. P.O. Box 302 Naperville, IL	Hillside, IL	2,4-D and esters and salts (I)* Silvex and esters and salts (I)* 2,4,5-T and esters and salts (I)* MCPA (II)*
Gulf Oil Corp. (see Millmaster Onyx)		
Hercules, Inc. 910 Market St. Wilmington, DE 19899	Brunswick, GA	2,4,5-T and esters and salts (I)* 2,4,5-Trichlorophenol and salts (I)*
Hooker Chemical Corp. 1900 St. James Pl. Houston, TX 77027 (Subsid. of Occidental Petroleum Corp.)	Niagara Falls, NY	2,4,5-Trichlorophenol and salts (I)* Lindane (II)
Imperial, Inc. West 6th and Grass Streets Shenandoah, IA	Shenandoah, IA	2,4-D and esters and salts (I)
Mallinckrodt, Inc. 675 Brown Rd. P.O. Box 5840 St. Louis, MO 63134	Raleigh, NC	Triiodobenzoic acid (II)*

(continued)

TABLE A7. (continued)

Producer	Location	Chemical (class)
Merck and Co., Inc. 126 East Lincoln Av. Rahway, NJ 07065	Hawthorne, NJ	Pentachlorophenol and salts (I)*
Miller Chem. and Fertz. Corp. Subsid. of Alco Standard Corp. Valley Forge, PA 19481	Whiteford, MD	2,4-D and esters and salts (I)*
Millmaster Onyx Group 99 Park Av. New York, NY 10016 (Part of Gulf Oil Corp.)	Berkeley Hgts., NJ	Silvex and esters and salts (I)*
		2,4,5-T and esters and salts (I)*
Mobil Chem. Co. Phosphorus Div. P.O. Box 26638 Richmond, VA 23261 (Div. of Mobil Corp.)	Charleston, SC	Dichlofenthion (I)*
	Mt. Pleasant, TN	Bifenox (I)
		Dichlofenthion (I)*
Monsanto Co. 800 North Lindbergh Blvd. St. Louis, MO 63166	Anniston, AL	Parathion (II)
	Luling, LA	Propanil (II)*
	Nitro, WV	MCPA (II)*
	Sauget, IL	2,4-D and esters and salts (I)*
Monsanto Co. (continued)		Pentachlorophenol and salts (I)
		o-Benzyl-*p*-chlorophenol (II)
		MCPB (II)*
		PCNB (II)*
Morton Chem. Co. Div. of Morton-Norwich Products, Inc. 100 North Wacker Dr. Chicago, IL 60606	Ringwood, IL	Mecoprop (II)*
North Eastern Pharmaceutical and Chem. Co. P.O. Box 270 Stamford, CT 06904	Verona, MO	2,4,5-Trichlorophenol and salts (I)*
Occidental Petroleum Corp. (see Hooker)		
Olin Corp. 120 Long Ridge Rd. Stanford, CT 06904	Leland, MS	PCNB (II)
	McIntosh, AL	PCNB (II)
	Rochester, NY	PCNB (II)*

(continued)

TABLE A7. (continued)

Producer	Location	Chemical (class)
PBI-Gordon Corp. 300 South Third St. Kansas City, KS 66118	Kansas City, KS	Dimethylamine salt of dicamba (I) 2,4,5-T and esters and salts (I) Mecoprop (II)
Prentiss Drug and Chem. Co., Inc. 363 Seventh Av. New York, NY 10001	Newark, NJ	Lindone (II)
Reichhold Chem., Inc. RCI Bldg. White Plains, NY 10603	Tacoma, WA	Pentachlorophenol and salts (I) *o*-Benzyl-*p*-chlorophenol (II)
Rhodia, Inc. 600 Madison Av. New York, NY 10022 (Subsid. of Rhone-Poulenc SA [France])	N. Kansas City, MO	2,4-D (I)* 2,4-DB (I)* Ioxynil (II)*
	Portland, OR	2,4-D (I) 2,4-DB (I)
Rhodia, Inc. (continued)		2,4-DP (I) Bromoxynil and esters (II) MCPA and derivatives (II) MCPB (II) Mecoprop (II)
	St. Joseph, MO	2,4-D and esters and salts (I) 2,4-DB and salts (I) Bromoxynil and esters (II) MCPA and derivatives (II) MCPB (II) Mecoprop (II)
	St. Paul, MN	2,4-D and esters and salts (I)* 2,4-DB (I)*
Riverdale Chem., Inc. 220 East 17th St. Chicago Hgts., IL 60411	Chicago Hgts, IL	2,4-D and esters and salts (I) Silvex and esters and salts (I) 2,4,5-T and esters and salts (I)
Sobin Chem., Inc. International Minerals and Chem. Corp. IMC Plaza Libertyville, IL 60048	Newark, NJ	Propanil (II)*
Sonford Chem. Co. Pure-Atlantic Hwy. Port Neches, TX 77651	Port Neches, TX	Pentachlorophenol and salts (I)* 2,3,4,6-Tetrachlorophenol (I)*
Stauffer Chem. Co. Westport, CT 06880	Cold Creek, AL	Carbophenothion (II)*
	Henderson, NV	Carbophenothion (II)
	Mt. Pleasant, TN	Parathion (II)*

(continued)

TABLE A7. (continued)

Producer	Location	Chemical (class)
Syntex Corp. (see Arapahoe)		
Tenneco Chems. Co. Park 80 Plaza West Saddle Brook, NJ 07662 (Part of Tenneco, Inc.)	Fords, NJ	2,3,6-Trichlorobenzoic acid and salts (II)* (2,3,6-Trichlorophenyl) acetic acid and sodium salt (II)*
Thompson Chems. Corp. 3028 Locust St. St. Louis, MO 63103	St. Louis, MO	2,4-D and esters and salts (I)* 2,4,5-T and esters and salts (I)*
Thompson-Hayward Chem. Co. 5200 Speaker Rd. P.O. Box 2383 Kansas City, KS 66110 (Subsid. of North American Philips Corp.)	Kansas City, KS	2,4-D and esters and salts (I) Silvex and esters and salts (I) 2,4,5-T and esters and salts (I)
Transvaal, Inc. Marshall Rd. P.O. Box 69 Jacksonville, AR 72076 (Subsid. of Vertac, Inc.)	Jacksonville, AR	2,4-D and esters and salts (I) 2,4-DP (I) Silvex and esters and salts (I) 2,4,5-T and esters and salts (I) 2,3,4,6-Tetrachlorophenol (I) 2,4,5-Trichlorophenol and salts (I)
Union Carbide Corp. 270 Park Av. New York, NY 10017 (see also Alchem)	Institute and South Charleston, WV	Disul sodium (I)*
Uniroyal, Inc. 1230 Av. of the Americas New York, NY 10020	Naugatuck, CT	Chloranil (I)* Dichlone (II)*
Velsicol Chem. Corp. 341 East Ohio St. Chicago, IL 60611 (Subsid. of Northwest Industries, Inc.)	Bayport, TX Beaumont, TX	Parathion (II)* Dicamba (I)
Vertac, Inc. (see Transvaal and Eagle River)		
Vulcan Materials Co. P.O. Box Birmingham, AL 35223	Wichita, KS	Pentachlorophenol and salts (I)

(continued)

TABLE A7. (continued)

Producer	Location	Chemical (class)
Woodbury Chems. Subsid. of Comutrix Corp. 8373 N.E. 2nd Av. Miami, FL 33138	Orlando, FL	2,4-D and esters and salts (I)

*No longer produced at this location.

TABLE A8. FORMER PESTICIDE PRODUCTION LOCATIONS

Producer	Location	Chemical (class)
Aceto	Flushing, NY	Dichlone (II)
Amchem	Ambler, PA	Disul sodium (I)
		2,3,6-Trichlorobenzoic acid and salts (II)
	Fremont, CA	Disul sodium (I)
		Ioxynil (II)
		MCPB (II)
	Linden, NJ	Disul sodium (I)
	St. Joseph, MO	Disul sodium (I)
American Cyanamid	Warners, NJ	Dicapthon (I)
		Parathion (II)
American Potash	Hamilton, MS	Parathion (II)
Arapahoe	Boulder, CO	Chloranil (I)
Chem. Insecticide Corp.	Metuchen, NJ	2,4-D and esters and salts (I)
		2,4,5-T and esters and salts (I)
		2,4,5-Trichlorophenol and salts (I)
Chempar	Portland, OR	2,4-D and esters and salts (I)
		2,4,5-T and esters and salts (I)
Diamond Shamrock	Newark, NJ	2,4,5-T and esters and salts (I)
		2,4,5-Trichlorophenol and salts (I)
		MCPA (II)
Dow	Midland, MI	Erbon (I)
		MCPB (II)
du Pont	Deepwater, NJ	2,3,6-Trichlorobenzoic acid and salts (II)
Eli Lilly	Indianapolis, IN	Piperalin (II)
FMC	Baltimore, MD	Tetradifon (II)
GAF	Linden, NJ	Disul sodium (I)
		2,4,5-Trichlorophenol and salts (I)
Guth Chem.	Hillside, IL	2,4-D and esters and salts (I)
		Silvex and esters and salts (I)
		2,4,5-T and esters and salts (I)
		MCPA (II)
Hercules	Brunswick, GA	2,4,5-T and esters and salts (I)
		2,4,5-Trichlorophenol and salts (I)

(continued)

TABLE A8. (continued)

Producer	Location	Chemical (class)
Hooker	Niagara Falls, NY	2,4,5-Trichlorophenol and salts (I)
Mallinckrodt	Raleigh, NC	Triiodobenzoic acid (II)
Merck	Hawthorne, NJ	Pentachlorophenol and salts (I)
Miller Chem.	Whiteford, MD	2,4-D and esters and salts (I)
Millmaster Onyx	Berkeley Hgts., NJ	Silvex and esters and salts (I)
		2,4,5-T and esters and salts (I)
Mobil	Charleston, SC	Dichlorofenthion (I)
Monsanto	Luling, LA	Propanil (II)
	Nitro, WV	MCPA (II)
	Sauget, IL	2,4-D and esters and salts (I)
		MCPB (II)
		PCNB (II)
Morton	Ringwood, IL	Mecoprop (I)
N. Eastern Pharm.	Verona, MO	2,4,5-Trichlorophenol and salts (I)
Olin	Rochester, NY	PCNB (II)
Rhodia	N. Kansas City, MO	2,4-D and esters and salts (I)
		2,4-DB and salts (I)
	Portland, OR	Ioxynil (II)
	St. Paul, MN	2,4-D and esters and salts (I)
		2,4-DB and salts (I)
Sobin Chem.	Newark, NJ	Propanil (II)
Sonford	Port Neches, TX	Pentachlorophenol and salts (I)
		2,3,4,6-Tetrachlorophenol (I)
Stauffer	Cold Creek, AL	Carbophenothion (II)
Tenneco	Fords, NJ	2,3,6-Trichlorobenzoic acid and salts (II)
		(2,3,6-Trichlorophenyl) acetic acid (II)
Thompson Chem.	St. Louis, MO	2,4-D and esters and salts (I)
		2,4,5-T and esters and salts (I)
Union Carbide	Institute and South Charleston, WV	Disul sodium (I)
Uniroyal	Naugatuck, CT	Chloranil (I)
		Dichlone (II)

(continued)

TABLE A8. (continued)

Producer	Location	Chemical (class)
Velsicol	Bayport, TX	Parathion (II)
	Chattanooga, TN	Dicamba (I)
Woodbury	Orlando, FL	2,4-D and esters and salts (I)

APPENDIX B
LITERATURE REVIEW

This appendix is a compilation of references on dioxin analysis categorized by sample matrix. The categories are given below:

- Air
- Biological tissue
- Blood
- Commercial chlorophenols
- Fats or oils
- Fish and crustaceans
- Flue gas
- Fly ash
- Grain
- Herbicide formulations
- Hexachlorobenzene
- Insecticides
- Milk or cream
- Plant material
- Soil
- Urine
- Water
- Wipe samples
- Wood

Air—

Oswald, E. 1979. Toxicology Research Projects Directory, Vol. 4, Iss. 7.

Biological Tissue—

Baughman, R., and M. Meselson. 1973. Environmental Health Perspectives, 5:27.

Bradlaw, J.A., et al. 1975. Proceedings of Society of Toxicology Meeting, Williamsburg, VA, March.

Freudenthal, J. 1978. In: Dioxin—Toxicological and Chemical Aspects, F. Cattabeni, A. Cavallaro, and G. Galli, eds., SP Medical and Scientific Books, NY, pp. 43–50.

Hass, J.R., et al. 1978. Anal. Chem. Vol. 50.

McKinney, J.D. 1978. In: Chlorinated Phenoxy Acids and Their Dioxins. Ecol. Bull., 27:53–66.

O'Keefe, P.W. 1978. In: Dioxin—Toxicological and Chemical Aspects. F. Cattabeni, A. Cavallaro, and G. Galli, eds., SP Medical and Scientific Books, NY, pp. 59–78.

Oswald, E. 1979. Toxicology Research Projects Directory, Vol. 4, Iss. 7.

Rose, J.Q., et al. 1976. Toxicol. Appl. Pharmacol., 36:209.

Shadoff, L.A., and R.A. Hummel. 1978. Biomed Mass Spectrom, 5(1):7–13, January.

Tiernan, T.O. 1976. EPA Contract No. 68-01-1959. December.

Woolson, E.A., R.F. Thomas, and P.D.J. Ensor. 1972. J. Agric. Food Chem., 20:351.

Woolson, E.A., et al. 1973. Advanced Chemistry Series.

Young, A.L. 1974. Report No. AFATL-TR-74-12, Air Force Armament Laboratory, Eglin Air Force Base, FL.

Blood—

Hummel, R.A. 1977. J. Agric. Food Chem., 25:1049-1053.

Oswald, E. 1979. Toxicology Research Projects Directory, Vol. 4, Iss. 7.

Commercial Chlorophenols—

Blaser, W.W., et al. 1976. Anal. Chem., 48:984.

Buser, J.R. 1975. J. Chromatography, 107:295.

Buser, J.R., and H.P. Bosshardt. 1976. Journal of the AOAC, 59:562.

Crummett, W.B., and R.H. Stehl. 1973. Environmental Health Perspectives, 5:15.

Firestone, D., et al. 1972. Journal of AOAC, 55:85.

Higginbotham, G.R., et al. 1968. Nature (London), 220:702.

Lamberton, J., et al. 1979. J. Amer. Ind. Hyg. Assoc., 40:816-822.

Langer, H.G., et al. 1971. 162d Meeting, ACS, Washington, DC, Pest. Sec., No. 83.

Micure, J.P., et al. 1977. J. Chromatogr. Sci., 7:275.

Pfeiffer, C. 1976. J. Chromatogr. Sci., 14:386.

Pfeiffer, C.D., T.J. Nestrick, and C.W. Kocher. 1978. Anal. Chem., 6:800.

Fats or Oils—

Campbell, T.C., and L. Friedman. 1966. Journal of the AOAC, 49:824.

Firestone, D. 1976. Journal of the AOAC, 59:323-325.

Firestone, D. 1977. Journal of the AOAC, 60:354-356.

Higginbotham, G.R., et al. 1967. Journal of the AOAC, 50:874.

Horwitz, W., ed. 1975. Official Methods of Analysis of the Association of Official Analytical Chemists, Association of Official Analytical Chemists, Washington, DC, 12th ed., Sect. 28.118, pp. 511-512.

Hummel, R.A. 1977. J. Agric. Food Chem., 25:1049-1053.

Kocher, C.W., et al. 1978. Bulletin of Environmental Contamination and Toxicology, 19:229.

O'Keefe, P.W., M.S. Meselson, and R.W. Baughman. 1978. Journal of the AOAC, 61:621-626.

Ress, J.R., G.R. Higginbotham, and D. Firestone. 1970. Journal of the AOAC, 53:628-634.

Shadoff, L.A., et al. 1977. Annali di Chimica, 67:583.

Shadoff, L.A., and R.A. Hummel. 1978. Bio. Mass Spec., 5:7.

Williams, D.T., and B.J. Blanchfield. 1971. Journal of the AOAC, 54:1429-1431.

Williams, D.T., and B.J. Blanchfield. 1972. Journal of the AOAC, 55:93-95.

Williams, D.T., and B.J. Blanchfield. 1972. Journal of the AOAC, 55:1358-1359.

Fish and Crustaceans—

Baughman, R.W., and M. Meselson. 1973. 166th Nat. Meeting, ACS, Chicago, Abstract Pest., 55.

Baughman, R.W., and M. Meselson. 1973. Environmental Health Perspectives, Expt. 5:27-35.

Baughman, R.W. 1974. Ph.D. Thesis, Harvard University, Cambridge, MA.

Fukuhara, K., et al. 1975. J. of Hyg. Chem., 21:318.

Gross, M.L. 1978. Personal communication. November.

Lamparski, L.L., T.J. Nestrick, and R.H. Stehl. Anal. Chem., 51(9):1453-1458.

Shadoff, L.A., and R.A. Hummel. 1975. 170th Nat. Am. Chem. Soc. Meeting, Chicago. Ab. Anal., Vol. 80.

Shadoff, L.A., et al. Bull. Environ. Contam. Toxicol. In press.

Flue Gas—

Frigerio, A., and M.C. Tagliabue. Impianti Incenerimento Rifuite Solidi: Prelievo, Anal. Controllo Effluenti, [conv.]; 59–71.

Fly Ash—

Buser, H.R., H.P. Bosshardt, and C. Rappe. 1978. Chemosphere, 2:165.

Grain—

Hummel, R.A. 1977. J. Agric. Food Chem., 25:1053–1099.

Isensee, A.R., and G.E. Jones. 1971. J. Agric. Food Chem., 19:1210.

Shadoff, L.A., and R.A. Hummel. 1978. Biomed Mass Spectrom, 5(1):7–13, January.

Herbicide Formulations—

Brenner, K.S., K. Muller, and P. Sattel. 1972. J. Chromatography, 64:39.

Brenner, K.S., K. Muller, and P. Sattel. 1974. J. Chromatography, 90:382–387.

Buser, H.R., and H.P. Bosshardt. 1974. J. Chromatography, 90:71.

Crummett, W.B., and R.H. Stehl. 1973. Environmental Health Perspectives, 5:15.

Edmunds, J.W., D.F. Lee, and C.M.L. Nickels. 1973. Pestic. Sci., 4:101.

Elvidge, D.A. 1971. Analyst (London), 96:721.

Hackins, J.N., D.L. Stalling, and W.A. Smith. 1978. Journal of the AOAC, 61:32.

Hohmstedt, B. 1978. In: Dioxin—Toxicological and Chemical Aspects. F. Cattabeni, A. Cavallaro, and G. Galli, eds., SP Medical and Science Books, NY, pp. 13–25.

Hughes, B.M., et al. 1975. Natl. Tech. Inform. Serv., AD-A011, 597:Vol. 1.

Polyhofer, K. 1979. Levensm Unters Forsch. 168(1):21–24, January.

Ranstad, T., N.H. Mahle, and R. Matalon. 1977. Anal. Chem., 49:386.

Rappe, C., H.R. Buser, and H.P. Bosshardt. 1978. Chemosphere, 5:431.

Shadoff, L.A., et al. 1978. Anal. Chem., 50(11):1586–1588.

Tiernan, T.O. 1976. EPA Contract No. 68-01-1959, December.

Tiernan, T.O., M.L. Taylor, and B.M. Hughes. 1975. Proceedings 1975 International Controlled Release Pesticide Symposium.

Vogel, H., and R.D. Weeren. 1976. Anal. Chem., 280:9.

Woolson, E.A., R.F. Thomas, and P.D. Ensor. 1972. J. Agric. Food Chem., 20:351.

Hexachlorobenzene—

Villanueva, E.C., et al. 1974. J. Agric. Food Chem., 22:916.

Insecticides—

Elvidge, D.A. 1971. Analyst, 96:721.

Storherr, R.W., et al. 1971. Journal of the AOAC, 54:218.

Webber, T.J.N., and D.J. Box. 1973. Analyst (London), 98:181.

Woolson, E.A., R.F. Thomas, and P.D.J. Ensor. 1972. J. Agric. Food Chem., 20:351.

Shadoff, L.A., et al. Bull. Environ. Contam. Toxicol. In press.

Shadoff, L.A., and R.A. Hummel. 1978. Biomed Mass Spectrom, 5(1):7–13 January.

Milk or Cream—

Baughman, R., and M. Meselson. 1973. Environmental Health Perspectives, Exp. Issue 5, 27–35.

Baughman, R.W. 1974. Ph.D. Thesis, Harvard University, Cambridge, MA.

Hummel, R.A. 1977. J. Agric. Food Chem., 25:1049–1053.

Plant Materials—

Buser, H.R. 1977. Anal. Chem., 49:918.

Buser, H.R. 1978. Monogr. Giovanni Lorenzini Found.; Vol 1, In: Dioxin—Toxicological and Chemical Aspects. F. Cattabeni, A. Cavallaro, and G. Galli, eds. SP Medical and Science Books, NY, pp. 27–41.

Di Domenico, A., et al. 1979. Anal Chem; 51(6):735–740.

Hummel, R.A. 1977. J. Agric. Food Chem., 25:1049–1053.

Shadoff, L.A., and R.A. Hummel. Biomed Mass Spectrom, 5(1): 7–13, January.

Soil—

Bertoni, G., et al. 1978. Anal. Chem., 6:732.

Buser, H.R. 1977. Anal. Chem., 49:918.

Buser, H.R. 1978. Monogr. Giovanni Lorenzini Found.; Vol 1, In: Dioxin—Toxicological and Chemical Aspects. F. Cattabeni, A. Cavallaro, and G. Galli, eds., SP Medical and Science Books, NY, pp. 27–41.

Camoni, I. 1978. J. of Chromatography, 153:233–238.

Di Domenico, A., et al. 1979. Anal Chem., 51(6):735–740.

Gross, M.L. 1978. Personal communication. November.

Hummel, R.A. 1977. J. Agric. Food Chem., 25:1049–1053.

Kearney, P.C., E.A. Woolson, and C.P. Ellington. 1972. Environ. Sci. Technol., 1017.

Nash, R.G. 1973. Journal of the AOAC, 56:728.

Shadoff, L.A., and R.A. Hummel. 1975. 170th National American Chemical Society Meeting, Chicago, IL, Abst. Anal., 80.

Shadoff, L.A., et al. Bull. Environ. Contam. Toxicol. In press.

Shadoff, L.A., and R.A. Hummel. 1978. Biomed Mass Spectrom, 5(1):7–13, January.

Widmark, G. 1971. Tracer Cosmos, a Realistic Concept in Pollution Analysis. In: International Symposium on Identification and Measurement of Environmental Pollutants, B. Westley, ed. National Research Council of Canada, Ottawa, p. 396.

Woolson, E.A., et al. 1973. Advances in Chemistry Series, 120:112.

Urine—

Oswald, E. 1979. Toxicology Research Projects Directory, Vol. 4, Iss. 7.

Water—

Junk, G.A., et al. 1976. J. Am. Water Works Assoc., 68:218.

Shadoff, L.A., and R.A. Hummel. 1978. Biomed Mass Spectrom, 5(1):7–13, January.

Wong, A. 1978. EPA Contract No. 68-03-2678, July.

Wipe Samples—

Di Domenico, A., et al. 1979. Anal. Chem., 51(6):735–740.

Erk, S.D., M.L. Taylor, and T.O. Tiernan. 1979. Chemosphere, 8(1):7–14.

Wood—

Hass, J.R., et al. 1978. Anal. Chem., 50:1474.

Levin, J.D., and C.A. Nilsson. 1977. Chemosphere, 7:443.

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